CONTENTS

# The American Journal of Medicine

VOL. 1 NOVEMBER, 1946 No. 5

## *Clinical Studies*

Levels of Blood Pressure in Both Arms and Legs in Normal Subjects and Patients Suffering from Certain Diseases
HAROLD J. STEWART, ABBOTT A. NEWMAN AND WILLIS F. EVANS 451

An analysis of observations made on twenty-one normal subjects and 102 patients with a variety of cardiac lesions and other disorders. Blood pressure readings in the legs were found to be helpful particularly in the recognition of coarctation of the aorta.

Relative Importance of Certain Variables in the Clinical Determination of Blood Pressure . . . . . CHARLES E. KOSSMANN 464

A discussion of the effect on sphygmomanometric readings of variation in the position of the arm, its venous blood content, the thickness of the arm and the use of right or left arm.

Concentration of Renin in Renal Venous Blood in Patients with Chronic Heart Failure . . ARTHUR J. MERRILL, J. L. MORRISON AND EMMETT S. BRANNON 468

Renin in significant amount was demonstrated in renal venous blood obtained from patients with chronic heart failure. The observation affords an interesting explanation for hitherto obscure vasoconstrictor phenomena occurring in association with congestive failure.

Relief of Pellagrous Glossitis with Synthetic Folic Acid . . . . . TOM D. SPIES 473

Folic acid was found to alleviate both macrocytic anemia and glossitis in the pellagrin; whereas liver extract affected only the macrocytic anemia, and nicotinic acid ameliorated only the glossitis.

Results from Subtotal Gastric Resection in Peptic Ulcer. The Internist's Viewpoint
T. Grier Miller and Joseph T. L. Nicholson 476

A critical evaluation of the results of subtotal gastrectomy in 113 closely followed patients with peptic ulcer.

Nisulfazole Treatment of Chronic Ulcerative Colitis. . . . RALPH H. MAJOR 485

A study of the effects of nisulfazole, a nitro analogue of sulfathiazole not readily absorbed from the intestinal tract, in thirty-seven patients with ulcerative colitis. The author obtained better results with this agent than with any other in his experience.

Rôle of Hyaluronidase in Human Infertility
RAPHAEL KURZROK, SAMUEL L. LEONARD AND HELEN CONRAD 491

The enzyme hyaluronidase, which is present in semen, is capable of dissolving the gel and dispersing the follicle cells surrounding recently ovulated mammalian ova, thus permitting penetration by the sperm. The authors measured the hyaluronidase content of human semen. Infertility associated with hyaluronidase-deficient specimens was treated, apparently successfully, by adding bull hyaluronidase to the deficient specimens which were then artifically inseminated; or by packing the enzyme into the cervix before coitus.

## *Reviews*

Pneumonia. Etiology, Diagnosis and Specific Treatment . . MAXWELL FINLAND 507

An authoritative analysis and summary of present knowledge of the bacterial and virus pneumonias, with special emphasis on the present status of treatment.

*Contents continued on page* 5

# Selective Bile Acid Therapy in Impaired Fat Digestion

Because of its complex composition, whole bile exerts a multiplicity of pharmacologic actions. When bile is administered for a single purpose, numerous other actions, often undesirable, must be tolerated.

With Degalol, c.p. deoxycholic acid, specificity of action is available. A normal constituent of human bile, Degalol represents the fraction principally concerned with fat digestion and absorption. In the dosage required, Degalol exerts little choleretic action, hence is especially superior when excessive biliary stimulation must be avoided.

Degalol is specifically indicated for the correction of impaired fat digestion and to promote absorption of the fat soluble vitamins D, E, and K, and carotene. It is useful in overcoming epigastric distress due to fatty foods, and should be given whenever fat digestion and absorption of the fat soluble vitamins is impaired, as for instance in catarrhal or obstructive jaundice.

DOSAGE
One or two 1½ gr. tablets t.i.d. Supplied in boxes of 100 sani-taped tablets.

**Degalol** REG U.S. PAT OFF

CHEMICALLY PURE DEOXYCHOLIC ACID

**Riedel-de Haen**

DIVISION OF AMES COMPANY, INC.

NEW YORK 13, N. Y.

CONTENTS

# The American Journal of Medicine

VOL. 1 NOVEMBER, 1946 No. 5

*Contents continued from page 3*

Curare. A Review of Its Therapeutic Effects and Their Physiological Basis
EDWARD B. SCHLESINGER 518

A timely summary of the present status of tubocurarine preparations, including short-acting aqueous solutions and long-acting suspensions in oil and wax. The physiological basis of paralyzant effects and of lissive or relaxant effects is discussed.

## *Seminar on the Therapeutic Use of Antibiotics*

Chemotherapy and Antibiotics in the Treatment of Meningitis
YALE KNEELAND, JR. 531

The author has drawn upon his large experience in both Army and civilian life to present a lucid account of the purulent meningitides (meningococcal, pneumococcal, streptococcal and H. influenzal) and their treatment: when and how to use sulfonamides, penicillin and streptomycin.

## *Conference on Therapy*

Treatment of Coronary Artery Disease (Concluded) . . . . . 539

Conferences on Therapy (Cornell University Medical College)—Part II of a spirited discussion of certain controversial aspects of the treatment of coronary artery disease. These include the duration of bed rest and the use of morphine, atropine, papaverine and other drugs in coronary thrombosis; the medical management of angina of effort and of the decubital form of angina; the use of paravertebral alcohol block, sympathectomy and rhizotomy.

## *Clinico-pathological Conference*

Purpura, Arthritis, Hepatomegaly and Hepatic Failure . . . . . 551

Clinico-pathological Conference (Washington University School of Medicine)—An interesting and difficult problem in diagnosis and classification.

## *Case Reports*

Agranulocytosis Occurring after Exposure to a D.D.T. Pyrethrum Aerosol Bomb
CLAUDE-STARR WRIGHT, CHARLES A. DOAN AND H. CAMPBELL HAYNIE 562

An instance of agranulocytosis which developed ten days after the use of a D.D.T. bomb, and responded to penicillin therapy.

Lupus Erythematosus Disseminatus in a Male
CAPT. W. CLAY DINE AND LIEUT. COL. C. STUART WILSON 568

An instructive case with unusually acute onset and varied symptomatology. The report includes necropsy findings.

Purulent Pericardial Effusion . . . . . MEYER TEXON 577

A fatal case of massive purulent pericardial effusion, with autopsy findings.

## *Editorial*

Vivax Malaria and the 8-Aminoquinolines . . . . . JAMES A. SHANNON 581

# General Information

THE AMERICAN JOURNAL OF MEDICINE extends an invitation to the profession for original releases on clinical investigations, clinical reviews, case reports and articles designed for postgraduate teaching.

Articles are accepted for publication with the understanding that they are original contributions never previously published. All manuscripts are subject to editorial modification, and upon acceptance become the property of THE AMERICAN JOURNAL OF MEDICINE.

THE AMERICAN JOURNAL OF MEDICINE does not hold itself responsible for any statement made or opinions expressed by any contributor in any article published in its columns.

A reasonable number of illustrations are supplied free of cost; special arrangements must be made with the editor and publishers for excess illustrations and elaborate tables.

Reprints are furnished on order. Prices are quoted on the first day of the month during which article appears. Individual reprints of an article must be obtained from the author.

Material published in THE AMERICAN JOURNAL OF MEDICINE is copyrighted and may not be reproduced without permission of the publishers.

Change of address must reach us by the 15th of the month preceding month of issue.

## PREPARATION OF MANUSCRIPTS

*Text.* Manuscripts are to be typewritten on one side of the paper, with double spacing and good margins. The original should be sent to the editor and a carbon copy retained by the author.

*Illustrations.* Illustrations must be in the form of glossy prints or drawings in black ink (*never* in blue). On the back of each illustration the figure number, author's name and an indication of the top of the picture should be given. Legends for illustrations are to be typewritten in a single list, with numbers corresponding to those on the photographs and drawings. Please do not attach legends to the pictures themselves.

*Bibliographies.* Bibliographic references should be at the end of the manuscript and not in footnotes. Each reference should include the following information in the order indicated: Name of author with initials; title of article; name of periodical; volume, page and year. The following may be used as a model:

BANCROFT, F. W., STANLEY-BROWN, M. and QUICK, A. J. Postoperative thrombosis and embolism. *Am J. Surg.*, 26: 648, 1945.

The subscription price of THE AMERICAN JOURNAL OF MEDICINE, is $10.00 per year in advance in the United States; $12.00 in Canada and foreign countries. Current single numbers $2.00. All Special Numbers $4.00. Prices for such back numbers as are available will be quoted on request.

*Address all correspondence to*

The American Journal of Medicine · 49 West 45th Street · New York 19

Benylate

BREON

is supplied in
4 oz., pint and
gallon bottles.

BREON

George A

# ITCH in 1800

may *have been palliated by assembly-line cooperation, as drawn by a humorist with Napoleon's army. For relief lasting a little longer, soldier and citizen* did *depend upon a mixture of lard and gunpowder.*

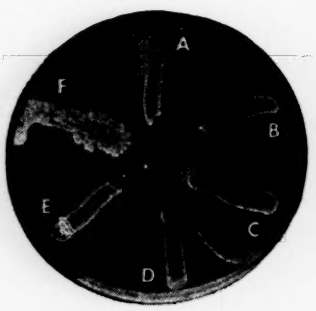
*The 1946 agent is BENYLATE-Breon. One application usually eradicates scabies as well as head lice and body lice.*

*Benylate is a lotion of benzyl benzoate 25% in triethanolamine stearate. White, cleanly, greaseless, it requires no dilution but is ready to apply for quick relief from itching; it penetrates skin crevices with lethal effect on mites.*

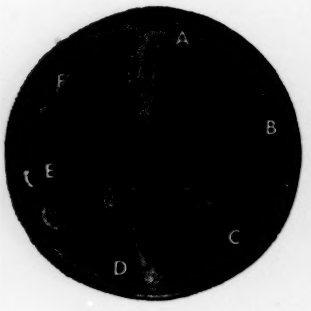
* Benylate is the trademark of

**Breon & Company**

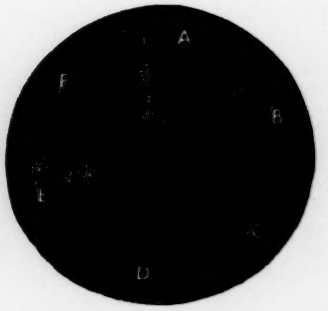
KANSAS CITY 10, MO.
NEW YORK
ATLANTA
LOS ANGELES
SEATTLE




0



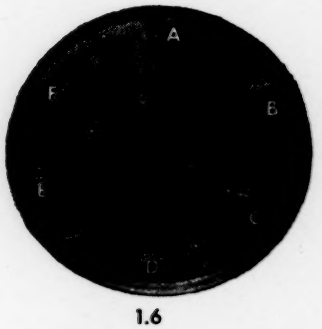

0.1



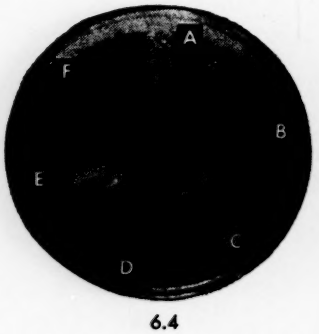

0.4

# Antibacterial Activity of STREPTOMYCIN

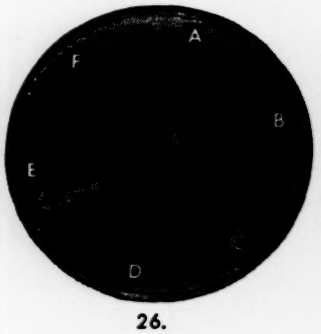
KEY TO PHOTOGRAPHS: • A. *Escherichia coli*
B. *Eberthella typhosa* • C. *B. proteus* • D. *Klebsiella pneumoniae*
E. *Bacillus pyocyaneus* • F. *Mycobacterium tuberculosis*
The numerals indicate micrograms of Streptomycin per cc. of agar.




1.6




6.4




26.

104.

THESE photographs show the inhibitory action of increasing concentrations of Streptomycin on a strain of six representative organisms *in vitro*. Inhibitory levels of concentration vary significantly with different strains.

Streptomycin exhibits a wide range of antibacterial activity *in vitro* and *in vivo* against both gram-positive and gram-negative organisms. Clinical results do not necessarily parallel *in vitro* activity or therapeutic results in experimental animals.

In clinical practice, Streptomycin is especially interesting because of its effectiveness against susceptible gram-negative organisms. The most noteworthy results to date have been obtained in the infections listed at the right.

*Our production of Streptomycin is being rapidly expanded. However, due to the present shortage, Streptomycin was placed on allocation by the Civilian Production Administration effective March 1, 1946. At present, civilian distribution may be authorized only by Dr. Chester Keefer, Evans Memorial Hospital, Boston, Mass., Chairman of the Committee on Chemotherapeutics and Other Agents of the National Research Council.*

**URINARY TRACT INFECTIONS**
due to susceptible
gram-negative organisms

**TULAREMIA**

**MENINGITIS**
due to *Hemophilus influenzae*

**WOUND INFECTIONS**
due to susceptible
gram-negative organisms

**MERCK & CO., Inc.** *Manufacturing Chemists* **RAHWAY, N. J.**

# *Reducing Renal Hazards*

# During Sulfonamide Therapy

**Almost complete freedom from kidney damage can be achieved by substituting COMBISUL-TD, a combination of *sulfathiazole* and *sulfadiazine* in equal parts, for either drug alone in equivalent whole dosage.**

**Both sulfathiazole and sulfadiazine can be dissolved simultaneously in the same solution nearly to the extent of the sum of their separate solubilities.[1,2] And because each compound behaves as though present alone in the solution the danger of intrarenal drug precipitation from the mixture is only as great as if each were administered alone, and in the partial dosage contained in the mixture. Therapeutic efficacy of COMBISUL-TD has proved to be the same as when either constituent is used alone in full dosage.**

# *Combisul-TD*

**COMBISUL-TD is available in 0.5 Gm. tablets each containing 0.25 Gm. sulfathiazole and 0.25 Gm. sulfadiazine. Indications and dosage are the same as for either drug administered alone.**

**COMBISUL-DM is available for the treatment of meningitis and consists of 0.25 Gm. sulfadiazine and 0.25 Gm. sulfameraxine.**

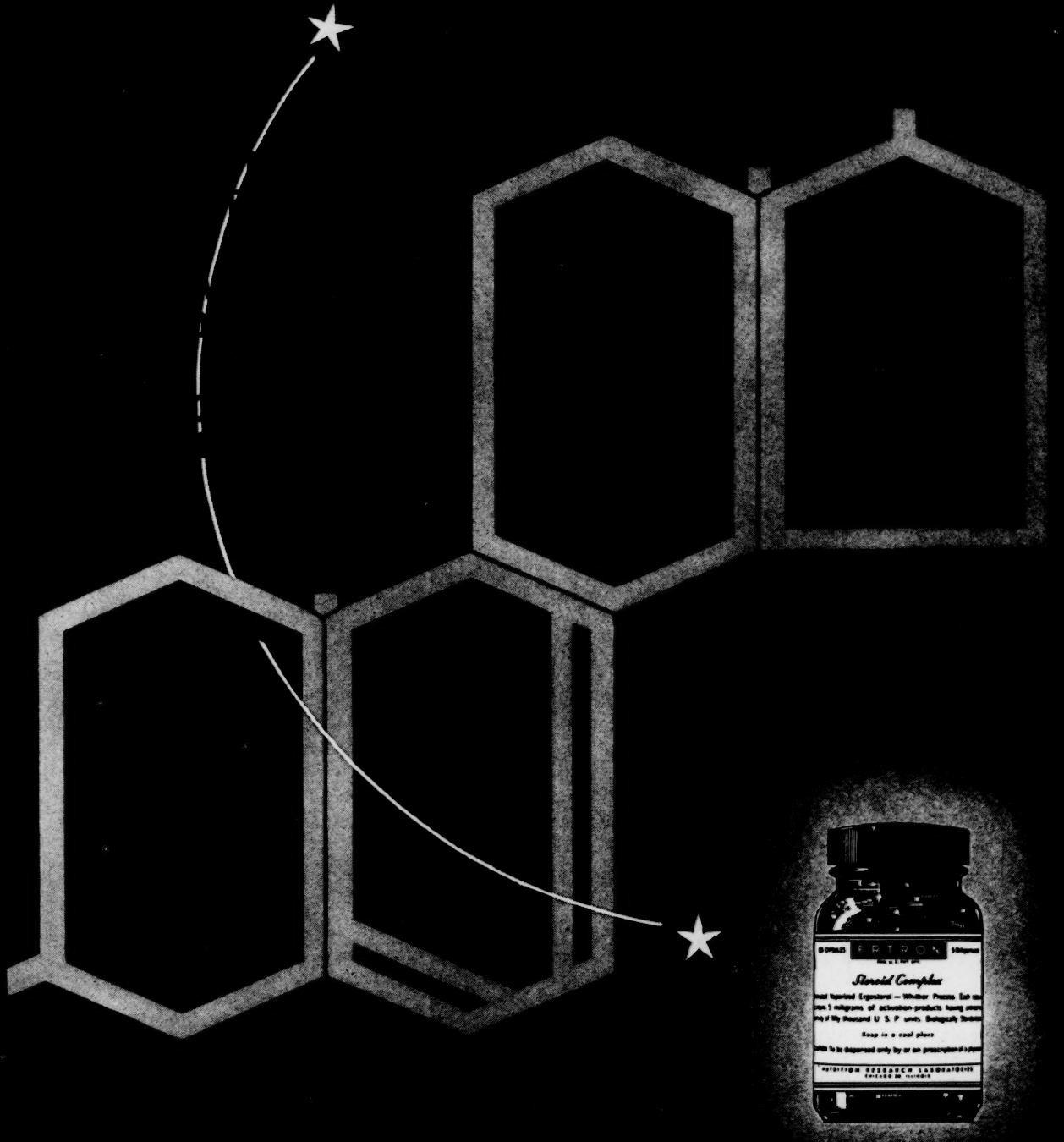
**COMBISUL-TD available in 0.5 Gm. tablets.**
**Bottles of 100 and 1,000 tablets.**

**COMBISUL-DM available in 0.5 Gm. tablets.**
**Bottles of 100 and 1,000 tablets.**

**BIBLIOGRAPHY:** (1) Lehr, D.: Proc. Soc. Exper. Biol. & Med. 58:11, 1945. (2) Lehr, D.: J. Urol. 55:548, 1946.

Trade-Marks COMBISUL-TD and COMBISUL-DM—Reg. U.S. Pat. Off.

*Schering* CORPORATION · BLOOMFIELD, N.J.
IN CANADA, SCHERING CORPORATION LIMITED, MONTREAL


ERTRON
Steroid Complex

# steroid therapy in arthritis

The findings of various investigators indicate that beneficial effects of Ertron—Steroid Complex, Whittier—are due to its systemic action. Under the regime of steroid therapy in arthritis as provided by Ertron, clinicians frequently observe in patients such subjective and objective responses as:

- Recession of pain
- Diminution of soft-tissue swelling
- Increased motility of the affected joints
- Improvement of function and resistance to fatigue
- A distinct feeling of well-being

The arthritic is enabled to increase his daily activities or to better withstand the surgical procedures of orthopedic restoration.

Laboratory studies over a five year period prove that Ertron—Steroid Complex, Whittier—contains a number of hitherto unrecognized components which are members of the steroid group. The isolation and identification of these substances in pure form establish the chemical uniqueness and steroid complex characteristics of Ertron. Each capsule of Ertron contains 5 milligrams of activation-products, biologically standardized to an antirachitic activity of fifty thousand U.S.P. Units.

Physician control of the arthritic patient is essential for optimum results. Ertron is available only upon the prescription of a physician.

**ETHICALLY PROMOTED**—Ertron is the registered trademark of Nutrition Research Laboratories. Supplied in bottles of 50, 100 and 500 capsules. Parenteral for supplementary intramuscular injection.

NUTRITION RESEARCH LABORATORIES • CHICAGO

anemias

anemia

anemia

anemia

Rx hepatinic

(McNeil)

—most readily assimilable form of iron (ferrous sulfate) combined with a unique, high-potency, predigested form of crude (unfractionated) liver concentrate—plus the factors of the vitamin B Complex—

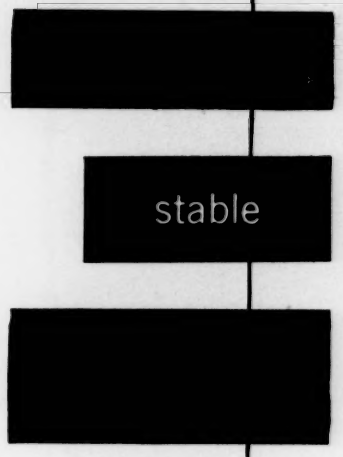
—a hematinic agent and nutritional supplement, which you can be sure your patients—young, old or middle-aged—will take and continue taking—

—has a delightful flavor—and the dosage is small: one teaspoonful t.i.d. Supplied in pints and gallons.

The alcoholic content of Hepatinic is very low—making it safe for pediatric use. Tasting samples available on request.

McNeil

**• Each fluidounce contains: Ferrous sulfate 12 gr., Crude Liver Concentrate 60 gr., fortified to represent Thiamine Hydrochloride 2 mg., Riboflavin 4 mg., Niacinamide 20 mg., together with pyridoxine, pantothenic acid, choline, folic acid, vitamin $B_{10}$, vitamin $B_{11}$, biotin, inositol, para-aminobenzoic acid and other factors of the vitamin B complex as found in crude (unfractionated) liver concentrate.**




Quicker acting, more penetrating and more stable than penicillin is tyrothricin, the nontoxic antibacterial principle of **'Prothricin'** Antibiotic Nasal Decongestant. Applied locally, tyrothricin promptly attacks bacteria, and its low surface tension promotes penetration of tissue crevices and mucosal folds.

Moreover, tyrothricin maintains antibiotic efficiency even in the presence of pus or mucus, and since (unlike penicillin) it is sparingly absorbed, local activity is prolonged.

In addition to tyrothricin (0.02%), **'Prothricin'** Antibiotic Nasal Decongestant contains an effective vasoconstrictor, 'Propadrine' hydrochloride* (1.5%), to help re-establish normal drainage without the unpleasant side-effects characteristic of ephedrine and its analogs.

Isotonic with normal nasal secretions, buffered in the physiologic pH range of 5.5-6.5, **'Prothricin'** decongestant is clear and free-flowing, does not impair ciliary function, and (unlike sulfonamide suspensions) does not form mucosal crusts that may block drainage.

Finally, **'Prothricin'** Antibiotic Nasal Decongestant is stable, retaining full antibacterial potency indefinitely at room temperature. This unique preparation is indicated in the local treatment of sinusitis, rhinitis, coryza and nasal congestion.

*Supplied in 1-ounce, dropper-assembly bottles.*

Sharp & Dohme, Philadelphia 1, Pa.

*Council-Accepted

SHARP & DOHME

# 'PROTHRICIN'

*antibiotic nasal decongestant*

White
LABORATORIES, INC.

**BECAUSE . . .**

Effective in BOTH acute AND chronic otitis media.

Has enhanced antibacterial potency.

Diffuses more completely into infected tissues.

Effects micro-debridement by chemical action on necrotic tissues.

Promotes effective local analgesia—without impaired sulfonamide activity.

Is free from unphysiologic alkalinity or distressing side actions.

Rapidly controls noxious odor of purulent discharge.

White's Otomide is composed of 5% Sulfanilamide, 10% Urea (Carbamide) and 3% Anhydrous Chlorobutanol in a specially processed glycerin vehicle of unusually high hygroscopic activity.

Supplied in dropper bottles of ½ fluid ounce (15 cc.)


**BIBLIOGRAPHY**

Strakosch, E. A. and Clark, W. G.: Minn. Med., 26:276-282 (Mar.) 1943.
Tsuchiya, H. M. et al.: Proc. Soc. Exp. Biol. and Med., 50:262-266 (June) 1942.
McClintock, L. A. and Goodale, R. H.: U. S. Naval Med. Bull., 41:1057-1064 (July) 1943.
Mertins, P. S. Jr.: Arch. Otolaryng., 26:509-513 (Nov.) 1937.
Ashley, R. E.: Trans. Am. Acad. Ophth. and Otolaryng., 46:257-264 (July-Aug.) 1942.


White's

O

# Bad winter ahead for the pneumococci

STORMY DAYS are usually followed by sharp increases in the incidence of upper respiratory infections, often the prelude to pneumococcal pneumonia. Fortunately, physicians are prepared to combat the pneumococci with sulfonamides and penicillin.

Although sulfonamides are generally effective, problems sometimes arise in their administration. In the patient with cardiac or renal disease, it may be difficult to maintain proper fluid balance. This imbalance may lead to urinary tract complications. Others may experience untoward toxic effects or lack of response to the drug. In these cases, Penicillin, Lilly, is particularly valuable. While the intramuscular injection of 10 to 15 thousand units every three hours throughout the night and day might be helpful, doses of 20 thousand or more units at the same intervals are preferable. Penicillin, Lilly, is available in 20-cc. ampoules containing 100,000, 200,000, or 500,000 units.

ELI LILLY AND COMPANY, INDIANAPOLIS 6 INDIANA, U.S.A.

The American Journal of Medicine

VOL. 1 NOVEMBER, 1946 No. 5

# Levels of Blood Pressure in Both Arms and Legs in Normal Subjects and Patients Suffering from Certain Diseases*

HAROLD J. STEWART, M.D., ABBOTT A. NEWMAN, M.D. AND WILLIS F. EVANS, M.D.
NEW YORK, NEW YORK

When studies of the circulation in coarctation of the aorta first were undertaken in this clinic, we were unable to find in the literature adequate data relating to blood pressure values in all four extremities for comparison. During the course of these studies, measurements were made of the blood pressure in both upper and lower extremities of normal subjects and patients with cardiovascular and other disease states. These data form the basis of this report. It seemed appropriate to record these data since no other reports are available in which the blood pressure in the four extremities are recorded.

Before 1924, it was the prevailing opinion that no blood pressure difference existed between upper and lower extremities in normal human subjects. Some of the earliest studies in which blood pressures were taken in both arms and legs were made on cases of aortic regurgitation. Hill and his associates,[1,2] in 1909 and 1912, first demonstrated that in aortic regurgitation systolic pressures were uniformly higher in the leg than in the arm, a finding so constant that they considered it of diagnostic value. This was confirmed by Murray[3] in 1914 in nineteen cases of aortic insufficiency, in whom the average systolic thigh pressure exceeded the upper arm by 26 mm. The observations of Williamson[4] in 1921 in twenty-four patients with aortic incompetence showed a difference in the arm and leg readings in favor of a higher leg pressure in only fourteen patients. He concluded that the difference was largely due to arterial thickening. The investigations of Bazett[5] in 1924 demonstrated in dogs a higher systolic pressure in the femoral than in the brachial artery. Burdick and his associates in 1925,[6] using photographic methods for the simultaneous registration of systolic blood pressures in arm and thigh, found the systolic pressure in normal subjects constantly higher in the leg than in the arm. In a horizontal resting position, the average difference was 38 mm. higher in the thigh, and increased to 68 mm. with exercise. In 1929, Strang,[7] from a study of fifty-four normal subjects, observed blood pressure readings in the leg in all instances higher than in the arm, regardless of position, with an average difference of 33 mm. of mercury. Hamilton and others[8] in 1939 reported the blood pressure higher in the legs than in the arms in thirty subjects, and Cady[9] in the same year observed higher systolic pressures in the popliteal than in the brachial artery, the difference being most marked in hypertensive cases.

* From the Department of Medicine at the New York Hospital, and Cornell University Medical College, New York, N. Y. Supported by a grant from the John and Mary R. Markle Foundation.

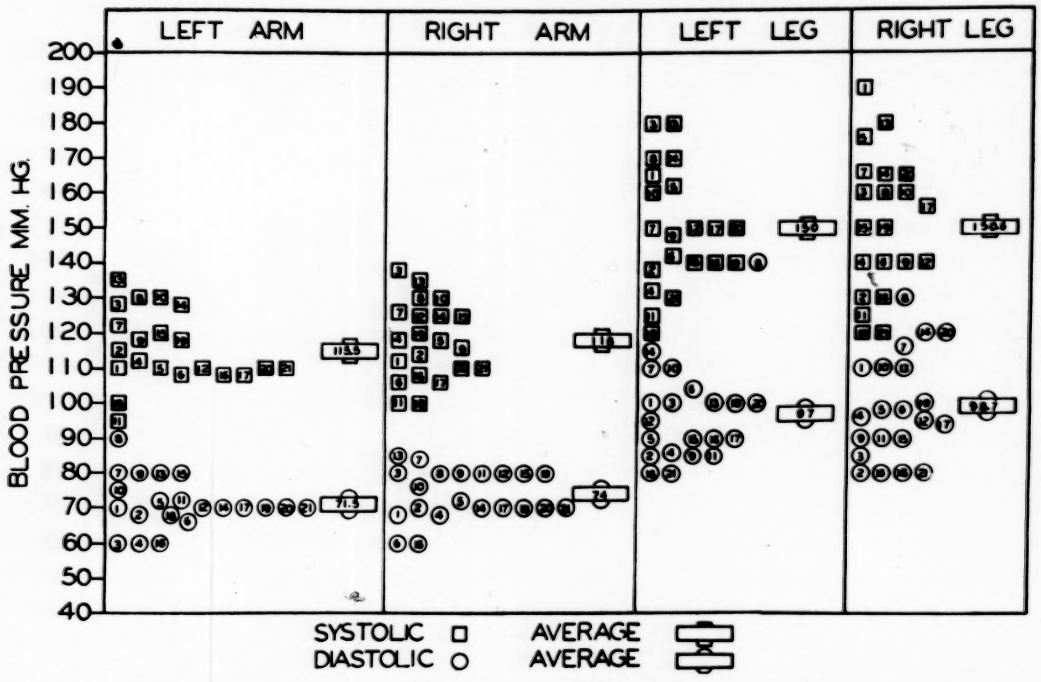



FIG. 1. In this figure are shown the measurements of blood pressure in the upper and lower extremities of twenty-one normal subjects, with average values for each extremity. In this illustration, as well as in Figures 2 to 8 inclusive, appropriate symbols identify systolic and diastolic levels and the average for the group. The numbers in each circle and square identify each patient. The average blood pressure for each extremity is recorded with the symbol for the average.

A study of the blood pressure in the lower extremity was made in 1943 by Wendkos and Rossman[10] in 500 soldiers between the ages of eighteen and thirty-five who had normal cardiovascular systems. They excluded those subjects in whom the blood pressure in the arm registered over 140 mm. systolic or 90 mm. diastolic. All pressures were recorded with the subject supine. In all cases the systolic blood pressure in the thigh (average 154.8 mm.) was greater than the corresponding blood pressure in the arm (average, 118.3 mm.) and the diastolic blood pressure in the thigh (average, 91.9 mm.) was either equal to or greater than the corresponding blood pressure in the arm (average, 70.6 mm.). The average difference in systolic blood pressure between arm and thigh was 36.5 mm., and the average diastolic difference 21.4 mm. Height of the subject did not appear to influence the average blood pressure in the thigh, although an increase in weight was associated with an increase in blood pressure in the lower extremity.

Gambill and Hines,[11] in 1944, studied blood pressures in the four extremities of 112 subjects with a wide variety of clinical states, but without significant vascular disease. They obtained an average systolic value in the arm of 115 mm. and in the thigh of 150 mm., with an average differential blood pressure of 35 mm. The diastolic blood pressure averaged 27 mm. higher in the thigh. The systolic blood pressure in the lower extremity showed the greatest tendency to vary from the average. The blood pressure averaged slightly higher in the right thigh than in the left.

Bazett[5] showed that the difference in systolic pressures in femoral and carotid arteries was exaggerated when aortic regurgitation was experimentally produced. In 1944, Kotte, Iglauer and McGuire[12]

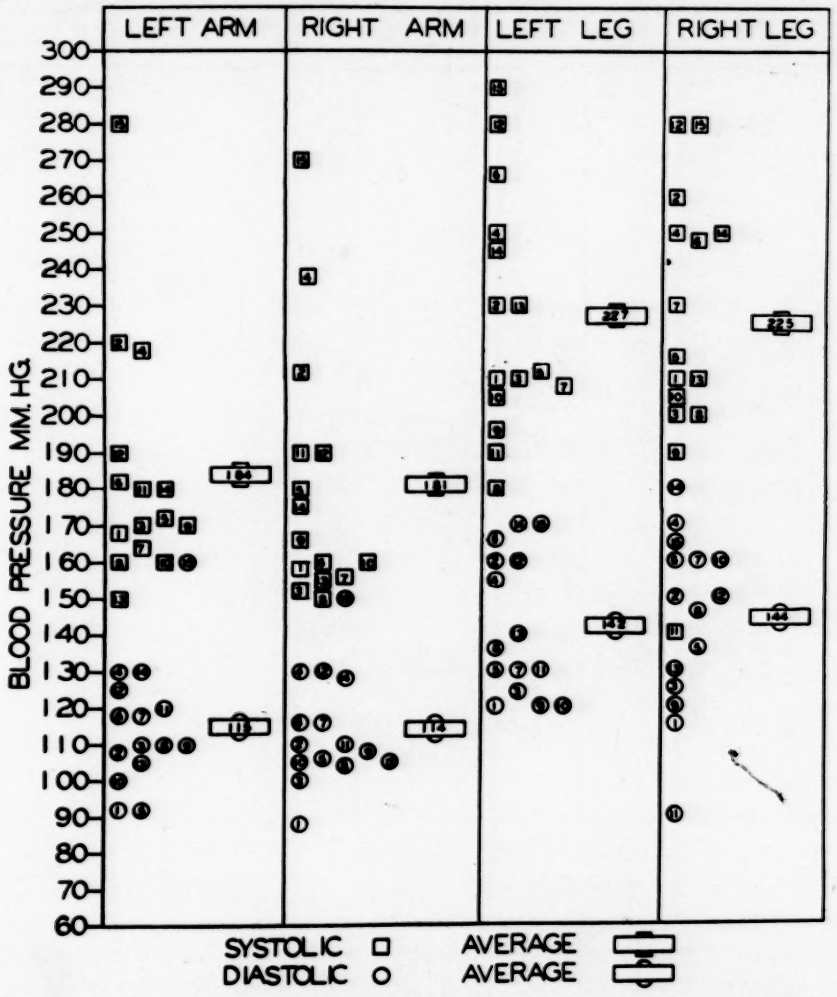



FIG. 2. In this figure the measurements of blood pressure are shown in the upper and lower extremities of fifteen cases of hypertension, with average values for each extremity.

measured the blood pressure in subjects with normal blood pressure, hypertension and aortic insufficiency, using the cuff method as well as an optical manometer. They found the femoral systolic pressure more frequently elevated in cases of aortic regurgitation, with differences usually greater than in hypertensive or "normotensive" groups.

Taussig,[13] in 1916, investigated blood pressures in patients with exophthalmic goiter, and found both systolic and pulse pressures in the leg substantially higher than in the arm. The differential systolic pressure averaged 37.3 mm. and the diastolic 7.6 mm. higher in the leg. The blood pressure differences in exophthalmic goiter were considered of the same type as in aortic regurgitation though of less degree.

The excellent collection of cases of coarctation of the aorta by King[14] in 1937 includes fifty-six adults in whom blood pressure measurements were recorded in all four extremities. The systolic pressures averaged 67 mm. higher in the upper extremity than in the leg. In twelve typical cases of coarctation, King found that ten had an absolute hypertension in the arms; in only one case was it normal. Steele[15] noted the frequent elevation of diastolic

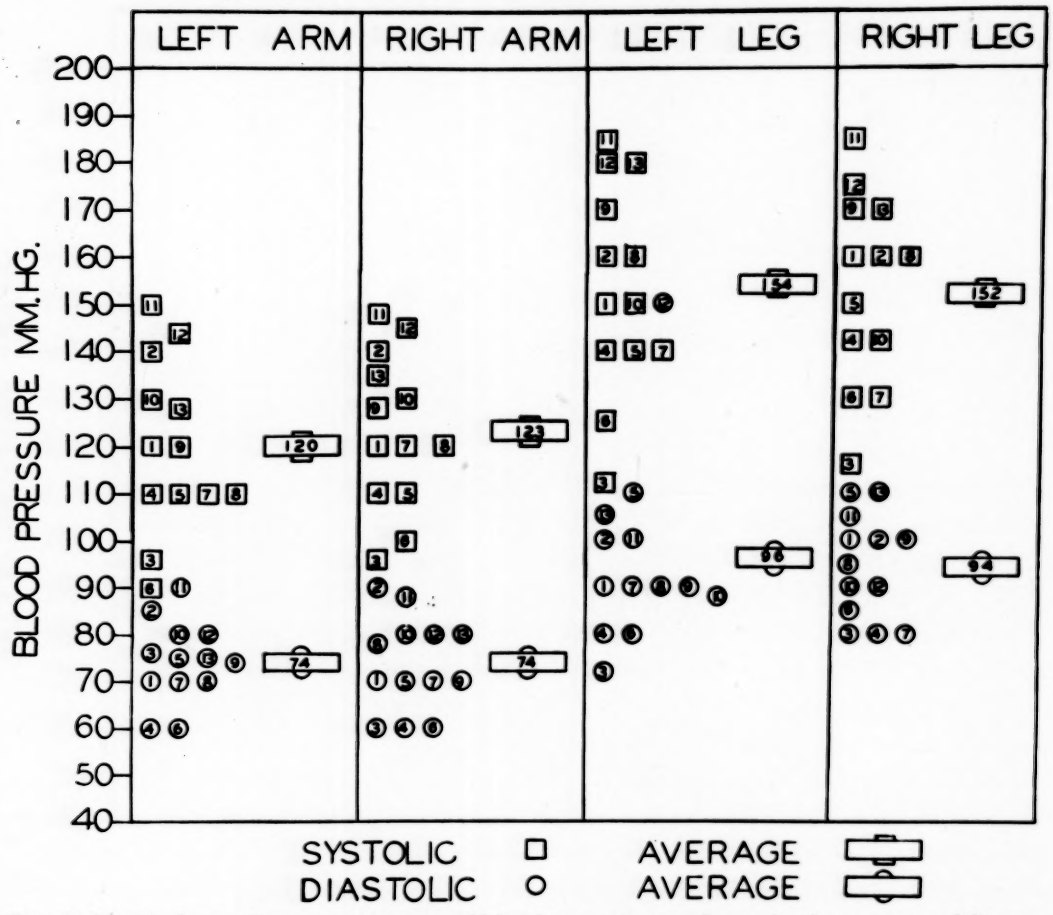



FIG. 3. In this figure the measurements of blood pressure are shown in the upper and lower extremities of thirteen patients with rheumatic heart disease, having mitral stenosis and insufficiency, but without involvement of the aortic valve. Average values are given for each extremity.

pressure in the legs, often approximating that of the arms in cases of coarctation of the aorta, and postulated an increase in peripheral arteriolar tone similar to that in essential hypertension. In fourteen cases studied by Stewart and Bailey[16] in 1941, all but one showed a higher systolic pressure in the arms than in the legs, and of eleven patients, three had higher diastolic pressures in the legs, four approximately equal diastolic pressure in the arms and legs, and three exhibited a higher diastolic pressure in the arms. In studying peripheral blood flow in cases of coarctation, Stewart, Haskell and Evans[17] found the blood pressure in the arms considerably higher than in the lower extremities, obtaining readings as high as 200/100 mm. in the right arm. They also observed wider pulse pressures in the upper extremities than in the legs.

## OBSERVATIONS

Measurements of blood pressure were made in all four extremities of 123 subjects ranging in age from eleven to seventy years.* All observations were made under basal conditions. Before readings were taken the subjects were kept at rest in a horizontal position for at least one-half hour in a room with constant temperature and humidity. A standard 5-inch blood-pressure cuff connected to a mercury manometer

* All blood pressure measurements were taken by H. J. Stewart and W. F. Evans.

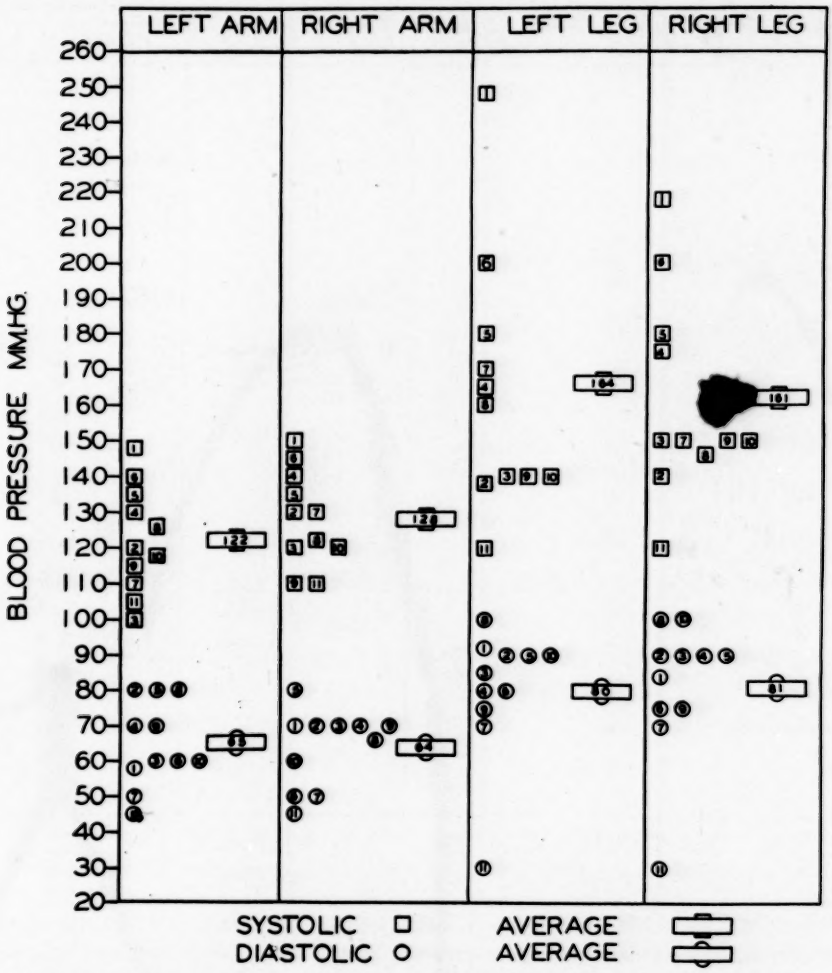



FIG. 4. In this figure the measurements of blood pressure are shown in the upper and lower extremities of eleven patients with rheumatic heart disease, having mitral stenosis and insufficiency and also aortic insufficiency. The patients in cases 3, 5, 6 and 11 had aortic stenosis as well. Average values are given for each extremity.

was used for both the arm and the thigh. Ballooning and displacement of the cuff was prevented by wrapping a towel securely around it. The pulse rate was recorded, and blood pressure readings were taken in the horizontal position. The level at which the first sound appeared was taken as the systolic pressure, and the point at which the sounds became suddenly muffled or disappeared was regarded as the diastolic pressure, as recommended by the American Heart Association.[18] In taking the blood pressure in the legs in patients with coarctation of the aorta, these changes may be heard for only a few beats. In a number of instances several readings were made, the last was then usually taken as representing the most accurate figure.

Observations were made on twenty-one normal subjects, fifteen patients with hypertension, twenty-three patients with coarctation of the aorta, thirteen patients suffering from rheumatic heart disease with mitral stenosis and insufficiency, eleven patients exhibiting rheumatic heart disease with mitral stenosis and insufficiency and also aortic insufficiency (including five patients who also had aortic stenosis) eleven subjects

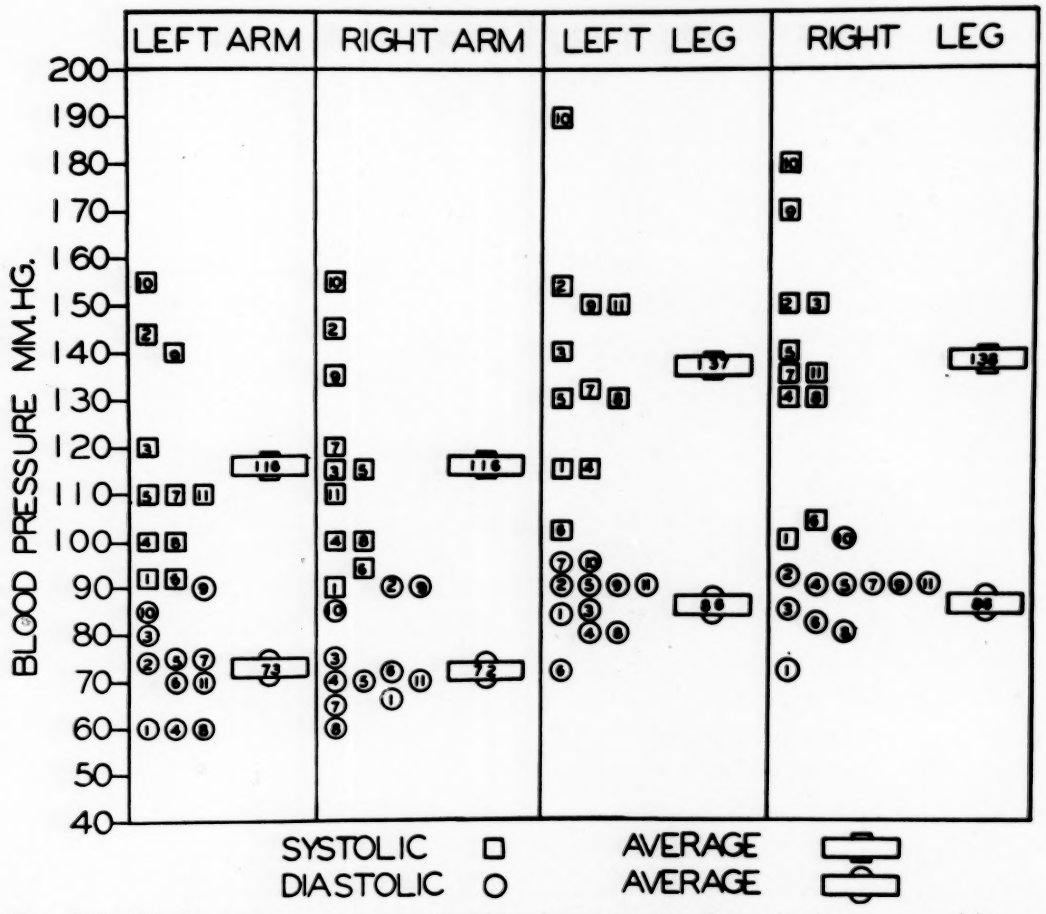



FIG. 5. In this figure the measurements of blood pressure are shown in the upper and lower extremities of eleven patients having congenital heart disease, with average values for each extremity. The patient in Case 1 suffered from pulmonary stenosis with interventricular septal defect, in Case 3 from pulmonary stenosis, in Case 4 from patent ductus arteriosus or foramen ovale, in Cases 2, 5, 6, 7, 8, 9 and 10 from interventricular septal defect.

with congenital heart disease, ten patients with Graves's disease and nineteen patients exhibiting a variety of other diseases.

The blood pressure of the four extremities for all patients in each group, as well as the averages for the group are shown in Figures 1 to 8 inclusive. In Figure 9 the average blood pressure values in each extremity are shown for all rubrics.

*Normal Subjects.* The measurements of blood pressure in the upper and lower extremities of twenty-one normal subjects are shown in Figure 1. The ages ranged from nineteen to twenty-seven, except patients number 10 and 21 who were forty-six and fifteen years of age, respectively. In the left arm a systolic range of 95 to 135 mm., with an average of 115.5 mm., and in the right arm a systolic range of 100 to 138 mm. with an average of 118 mm., were obtained. The diastolic pressure in the left arm ranged from 60 to 90 mm., averaging 71.5 mm.; in the right arm it ranged from 60 to 84 mm., averaging 74 mm. In the left lower extremity the systolic pressure ranged between 120 and 180 mm., averaging 150 mm., and in the right lower extremity it ranged between 120 and 190 mm., averaging 150.6 mm. The diastolic pressures in the legs were similarly elevated, in the left leg ranging from 80 to 140 mm., averaging 97 mm., in the right leg ranging from 80

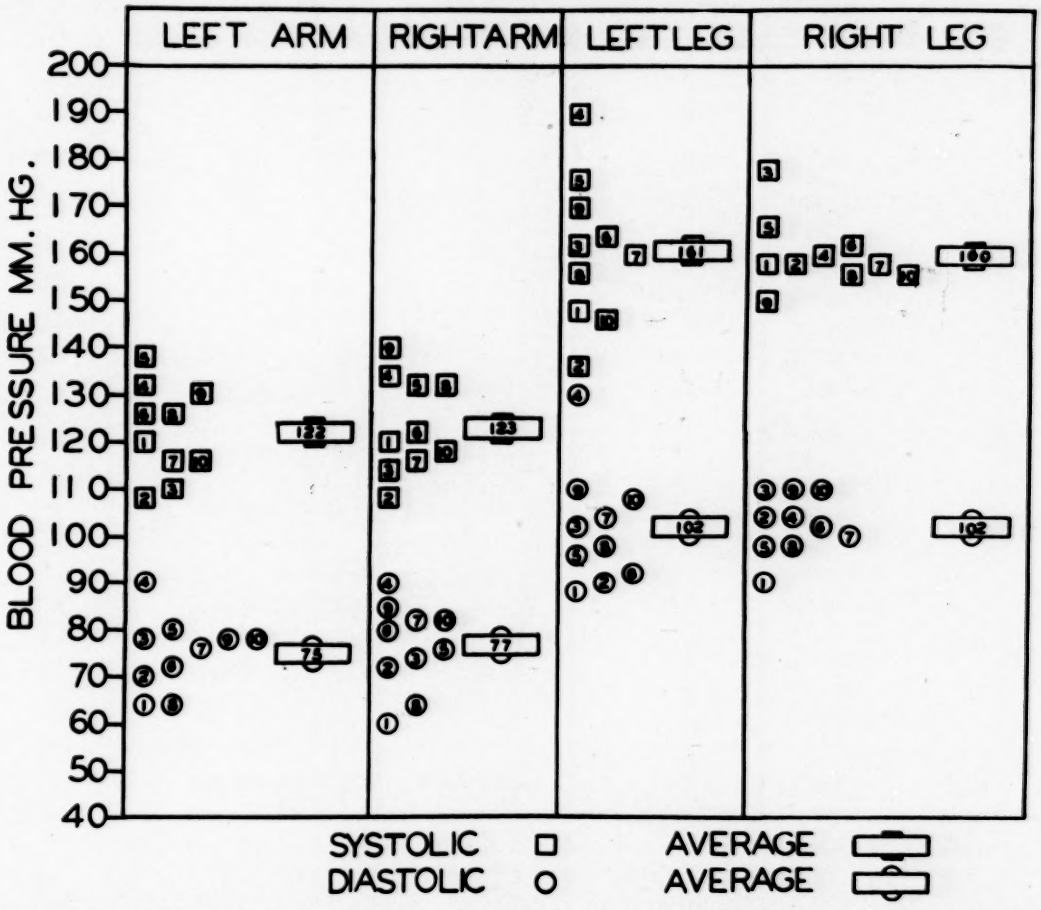



FIG. 6. In this figure the measurements of blood pressure are shown in the upper and lower extremities of ten patients with Graves's disease, with average values for each extremity.

to 130 mm., averaging 98.7 mm. Both the systolic and diastolic blood pressure in the legs were higher than those in the arms in every patient. Average blood pressures in both right extremities were higher than in the left.

*Hypertensive Patients.* In Figure 2 the blood pressure values, with averages, are plotted for each extremity in fifteen cases of hypertension. In the left arm a systolic range of 150 to 280 mm., with an average of 184 mm., and in the right arm a systolic range of 150 to 270 mm., with an average of 181 mm. were obtained. The diastolic pressure in the left arm ranged from 92 to 160 mm., averaging 115 mm., in the right arm it ranged from 88 to 150 mm., averaging 114 mm. In the left thigh, the systolic pressure ranged between 180 and 290 mm., averaging 227 mm., and in the right thigh it ranged between 140 and 280 mm., averaging 225 mm. The diastolic pressures in the left lower extremity fell in a range between 120 and 170 mm. with an average of 142 mm., in the right lower extremity the value ranged between 90 and 180 mm., averaging 144 mm. Systolic and diastolic blood pressures in the legs were higher than in the arms in the cases of hypertension.

Patients with rheumatic heart disease were separated into two groups, namely, those exhibiting mitral stenosis and insufficiency but without involvement of the aortic valve, and those with mitral valve lesions together with involvement of the aortic valve.

*Rheumatic Heart Disease without Aortic Insufficiency.* In Figure 3 the blood pressure

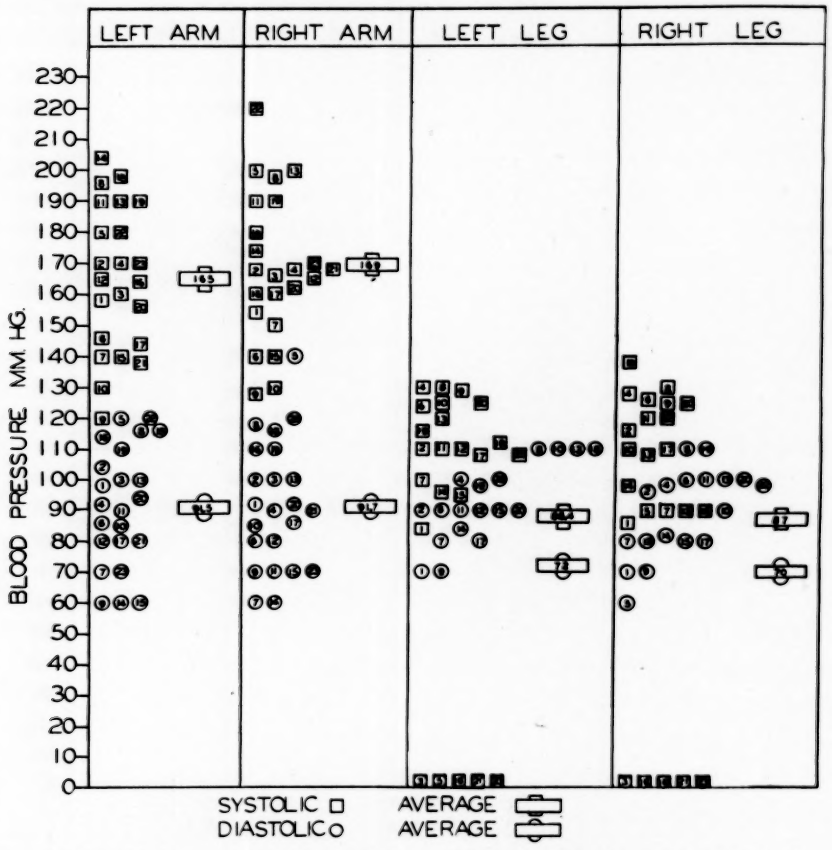



FIG. 7. In this figure the measurements of blood pressure are shown in the upper and lower extremities of twenty-three patients exhibiting coarctation of the aorta, with average values for each extremity.

readings are shown for thirteen cases with mitral disease without aortic involvement. Systolic pressures ranged from 90 to 150 mm., averaging 120 mm. in the left arm, and from 96 to 150 mm., averaging 123 mm., in the right arm. Diastolic pressures ranged from 60 to 90 mm., averaging 74 mm. in both arms. In the left lower extremity, systolic pressures ranged from 114 to 185 mm., averaging 154 mm. In the right lower extremity they ranged from 116 to 185 mm., averaging 152 mm. The diastolic pressures in the left leg ranged between 72 and 150 mm., with an average of 96 mm., and in the right leg diastolic pressures ranged from 80 to 110 mm., with an average of 94 mm. In short, in patients with rheumatic heart disease with mitral valve lesions only, higher systolic and diastolic blood pressures were obtained in the lower than in the upper extremity.

*Rheumatic Heart Disease with Aortic Insufficiency.* In Figure 4 the data relating to eleven patients with mitral stenosis and insufficiency, and aortic insufficiency of rheumatic etiology are shown. Four of the eleven patients also had aortic stenosis; these cases are indicated in the legend. In the left arm, the systolic range was from 100 to 148 mm., averaging 122 mm., in the right arm the range was from 110 to 150 mm., averaging 128 mm. The diastolic range in the left arm was 45 to 80 mm., with an average of 65 mm., in the right arm 45 to 80 mm., with an average of 64 mm. The systolic pressures in the left leg fell in a wide range between 120 and 248 mm., with an average of 164 mm.; in the right leg systolic pressures

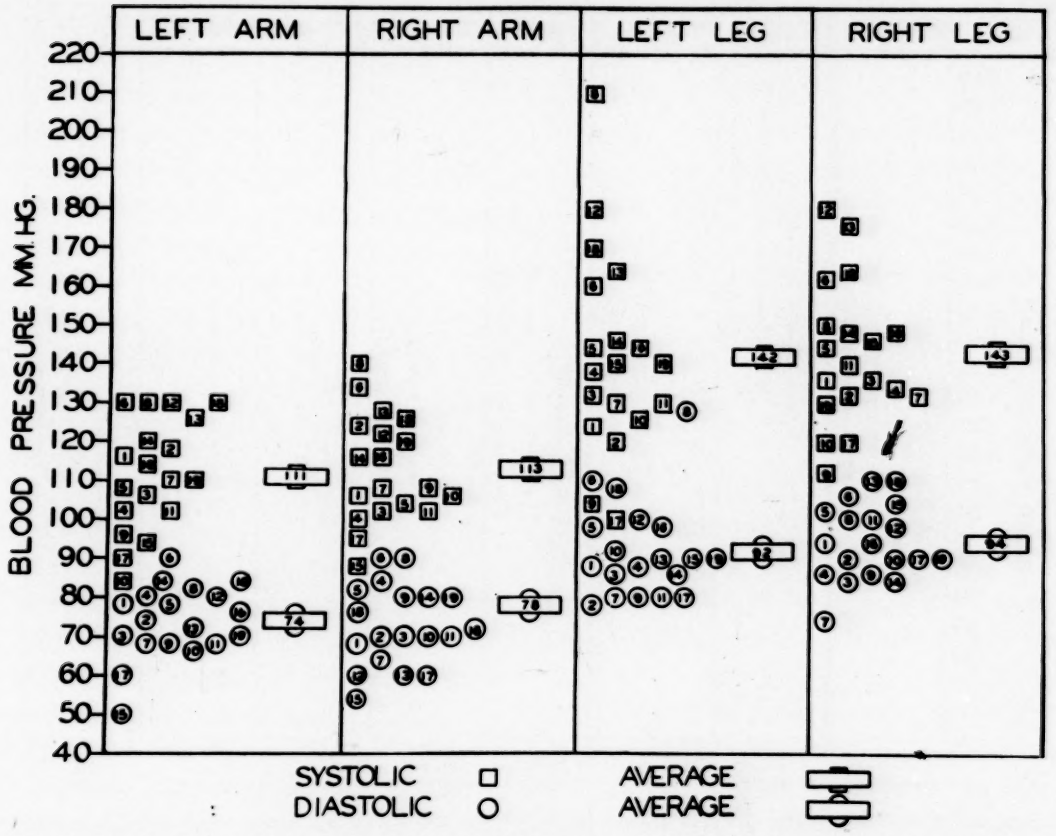



FIG. 8. In this figure the measurements of blood pressure are shown in the upper and lower extremities of nineteen miscellaneous patients having the following diseases: Patient No. 1 suffered from chronic constrictive pericarditis, No. 2 from suppurative arthritis, No. 3 from gastritis, No. 4 from disseminated lupus erythematosus, No. 5 from diabetes mellitus, No. 6 from sciatica, No. 7 from congenital syphilis, No. 8 from generalized arteriosclerosis, No. 9 from arteriosclerosis, No. 10 from carcinoma of the lung, No. 11 from Hodgkin's disease, No. 12 from diabetes mellitus, No. 13 from bronchiectasis, No. 14 from adrenal tumor (p. p.), No. 15 from myxedema, No. 16 from beriberi, No. 17 from chronic constrictive pericarditis, No. 18 from Raynaud's disease, and No. 19 from chronic constrictive pericarditis.

ranged from 120 to 218 mm., averaging 161 mm. Diastolic pressures in both lower extremities ranged from a low value of 30 mm. to 100 mm., averaging 80 mm. in the left leg and 81 mm. in the right leg. It appears, therefore, that in patients with mitral valve lesions and also aortic insufficiency of rheumatic origin, systolic and diastolic blood pressures in the legs are higher than in the arms, and average pulse pressure differences are wider than in cases with mitral valve lesions alone.

*Congenital Heart Disease.* Data relating to eleven patients suffering from congenital heart disease exclusive of coarctation of the aorta are shown in Figure 5. The diagnoses in each patient are shown in the legend. Septal defects were most common. They suffered from the following defects: Tetralogy of Fallot, pulmonary stenosis, patent foramen ovale, and interventricular septal defects. In the left arm the systolic pressure ranged between 92 and 155 mm., averaging 116 mm., and in the right arm between 90 and 155 mm., averaging 116 mm. The diastolic pressure in both arms ranged from 60 to 90 mm., averaging 73 mm. on the left and 72 mm. on the right. In the left leg systolic pressures fell in a range from 102 to 190 mm., averaging 137 mm., and in the

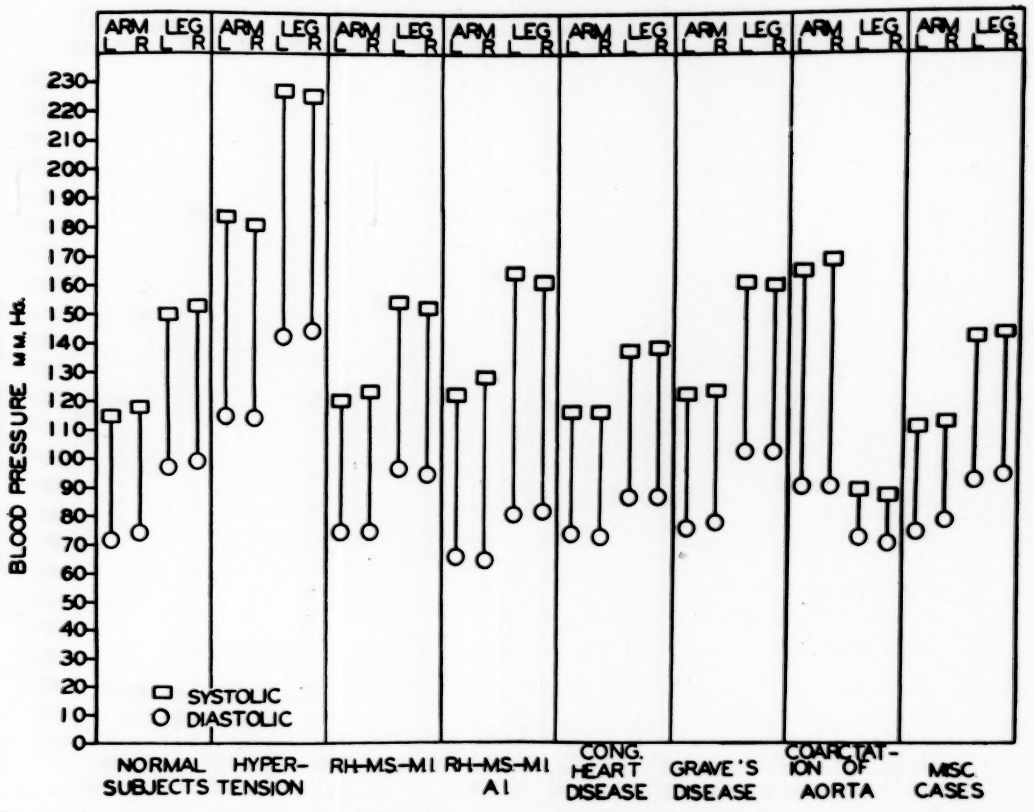



FIG. 9. In this figure the average blood pressures are shown in each extremity for all groups which were studied.

right leg from 100 to 180 mm., averaging 138 mm. Diastolic pressures ranged from 72 to 95 mm. in the left leg, and from 72 to 100 mm. in the right leg, averaging 86 mm. in both lower extremities. Systolic and diastolic blood pressures in the legs were higher than in the arms in all patients with congenital heart disease exclusive of coarctation of the aorta.

*Graves's Disease.* Observations made on ten patients with Graves's disease are shown in Figure 6. The systolic pressure in the left arm ranged from 108 to 138 mm., averaging 122 mm., and in the right arm from 108 to 140 mm., averaging 123 mm. In the left arm the diastolic pressure ranged from 64 to 90 mm., averaging 75 mm., and in the right arm from 60 to 90 mm., averaging 77 mm. The systolic pressures in the left leg ranged from 136 to 190 mm. with an average of 161 mm., in the right leg from 150 to 166 mm. with an average of 160 mm. Diastolic pressures ranged from 88 to 130 mm. in the left leg, from 88 to 110 mm. in the right leg, in both lower extremities averaging 102 mm. Systolic and diastolic blood pressures in the lower extremity were higher than in the arm in patients with Graves's disease and these values were higher than in normal subjects.

*Coarctation of the Aorta.* Data relating to twenty-three patients exhibiting coarctation of the aorta are shown in Figure 7. The systolic blood pressure in the left arm may be seen to range from 120 to 204 mm., averaging 165 mm., the systolic range in the right arm from 128 to 220 mm., averaging 169 mm. The diastolic pressure in the left arm ranged from 60 to 120 mm., averaging 91.5 mm., in the right arm from 60 to 120 mm., averaging 91.7 mm. In the lower left extremity the systolic pressure ranged from 0 (not obtainable) to 130 mm., averaging 88.4 mm., in the right lower extremity

from 0 to 138 mm., averaging 87 mm. Diastolic pressure in both legs ranged from 0 to 110 mm., with an average of 72 mm. in the left leg, and of 70 mm. in the right leg. Thus, in all except Case 9, systolic pressures in the upper extremity exceeded those in the legs.

*Miscellaneous Cases.* This group was made up of nineteen patients suffering from chronic constrictive pericarditis, suppurative arthritis, gastritis, disseminated lupus erythematosus, diabetes mellitus, sciatica, congenital syphilis, generalized arteriosclerosis, carcinoma of the lung, Hodgkin's disease, bronchiectasis, adrenal tumor, myxedema, beriberi and Raynaud's disease. The blood pressures are recorded in Figure 8 and the diagnoses are recorded in the legend. In the left arm the systolic range was from 90 to 130 mm. averaging 111 mm., and in the right arm 95 to 140 mm., averaging 113 mm. The diastolic range in the left arm was 50 to 90 mm., averaging 74 mm.; in the right arm it was 54 to 90 mm., averaging 78 mm. In the left leg the systolic pressure ranged from 100 to 210 mm., averaging 142 mm.; in the right leg the systolic pressure ranged from 112 to 180 mm., averaging 143 mm. Diastolic pressures in the left leg ranged from 78 to 128 mm., averaging 92 mm. In the right leg they ranged from 74 to 110 mm., averaging 94 mm. It is apparent that in each case both systolic and diastolic blood pressures were higher in the lower extremity than in the arm.

## COMMENTS

The blood pressure values which we obtained in the normal group show a close agreement with similar studies of other investigators. Our observations record separately the values in right and left extremity, while data found in most papers in the literature either represent aggregate values or else the specific arm or leg is not indicated. We found the blood pressures in both lower extremities in normal subjects higher than in the arms, the systolic difference averaging 33.6 mm. and the diastolic 25.1 mm. higher in the legs. As demonstrated previously by Amsterdam and Amsterdam,[19] the average blood pressure was noted to be several millimeters higher in the right extremity.

In fifteen cases of hypertension the same trend was observed. There was a greater difference in systolic pressure between arm and leg however, the systolic leg pressure averaging 43.5 mm. higher than the corresponding arm pressure. The diastolic difference was not as marked, averaging only 29 mm. higher in the legs.

In the cases of rheumatic heart disease with mitral valve lesions only, blood pressure values showed little difference from the normal group. The cases with aortic insufficiency, however, had wider pulse pressures in the upper extremity due in large part to a lower diastolic pressure in the arm. There was also a wider pulse pressure in the lower extremity, and this resulted from an average systolic leg pressure 10 mm. higher and a diastolic leg pressure 15 mm. lower than corresponding pressures in rheumatic cases with only mitral disease.

The blood pressure data in aortic incompetence reported by various observers are not in agreement as to blood pressure differences between upper and lower extremities. Murray[3] found a systolic difference of 26 mm. between arm and thigh, but no significant diastolic difference. Williamson[4] reported that fourteen of twenty-four cases of aortic incompetence showed a higher leg reading. In the remaining cases there was either a higher arm reading or no significant difference. Kotte, Iglauer and McGuire,[12] although observing higher femoral systolic pressures in seven of ten cases with aortic regurgitation, differences greater than in control and hypertensive groups, consider the 13 cm. arm band incapable of giving an accurate measurement of femoral systolic pressure.

The cases of congenital heart disease in our series did not show significant deviation from the normal. The reason why systolic and diastolic pressures in the lower extremities of these cases averaged only 11 to 13 mm. higher than in the arms (as compared to higher values in the normal) is not clear. No data on blood pressure differences in the extremities in congenital heart disease, with the exception of coarctation of the aorta, are found in the literature.

In our cases of Graves's disease, the systolic blood pressures in the upper extremity averaged 5 to 8 mm. higher than in the normal group, and the diastolic average in the arms was about 4 mm. higher than in the normal subjects. The pulse pressure in the upper extremity was not significantly increased. In the legs the average systolic pressure as well as the average diastolic pressure were higher than in the normal group. The systolic blood pressure difference between arm and leg was somewhat increased, averaging 38 mm. in cases of Graves's disease as compared to 33 mm. in normal subjects. The diastolic blood pressure difference between arm and leg averaged 26 mm. Taussig[13] obtained a systolic blood pressure difference between arm and leg of 37.3 mm. in nine cases of exophthalmic goiter, but the diastolic difference measured only 7.6 mm. The discrepancies may be partly due to the difficulty in accurately recording the diastolic blood pressure.

Our blood pressure findings in twenty-three cases of coarctation of the aorta are similar to those of other observers. Blood pressures in the arm were uniformly higher than in the legs. There was little difference between right and left extremity. Our values are considerably lower than those reported by King[14] in his study of fifty-six cases of coarctation, in which he obtained average systolic values of 189 mm. in the upper extremity and 123 mm. in the leg, and average diastolic values of 92 mm., and 91 mm. in arm and leg, respectively. The discrepancy may arise for several reasons: (1) Averages in King's fifty-six cases were made from a compilation of readings by a large number of observers while ours were made by two observers; (2) our series include many patients in whom sounds were inaudible in the lower extremity, and finally (3) all of our observations were made with the patients in a basal metabolic state.

It is recognized that blood pressures in the legs might also be significantly lowered in cases with marked narrowing or obstruction of the lumen of the vessels to the lower extremities. We did not come upon such patients, however, to use for comparison.

The necessity for taking blood pressure readings in the legs in every patient with systolic pressure over 135 mm., irrespective of age, if cases of coarctation are not to be overlooked is apparent from these observations. The above study serves to demonstrate the reliability, as a diagnostic finding, of the reversal in differential pressures in coarctation of the aorta. Because coarctation of the aorta was not recognized as the cause of hypertension such patients have been referred for splanchnic resection to lower the blood pressure. This is additional reason for measuring the blood pressure in the legs in a patient with elevated pressure. These patients should now be recognized for another reason: Crafoord and Nylin[20] and Gross and Hufnagel[21] have independently devised an operation to overcome the defect in coarctation of the aorta, namely, by resection of the constricted area with end-to-end anastomosis. Because these patients are subject to subacute bacterial endocarditis, rupture, aneurysmal dilatation and heart failure, they should be re-evaluated in the light of these recent advances.

## SUMMARY

1. Observations relating to the blood pressures recorded in all four extremities in 123 patients are presented.

2. In the following categories the systolic and diastolic blood pressures were higher in the legs than in the arms: normal subjects, those with hypertension, patients suffering from rheumatic heart disease with mitral stenosis and mitral insufficiency, and those with mitral stenosis and mitral insufficiency together with aortic insufficiency, patients suffering from congenital heart disease, (exclusive of coarctation of the aorta), patients suffering from Graves's disease and a group of patients with a variety of diseases.

3. Higher systolic and diastolic blood pressures were obtained in the arm than in the thigh in twenty-three cases of coarctation of the aorta, a reversal of the situation encountered in normal subjects and in patients suffering from the diseases listed above, indicating the importance of this finding as a diagnostic aid.

4. Patients with rheumatic heart disease with mitral stenosis and insufficiency and also aortic insufficiency show a wider pulse pressure in the lower extremity, due to higher average systolic and lower average diastolic pressures, than rheumatic cases with only mitral valve lesions.

5. Slightly lower average systolic and diastolic values for the lower extremity were obtained in cases of congenital heart disease (exclusive of coarctation of the aorta) than in the normal group.

6. In most groups, including the normal, both systolic and diastolic average pressures tend to be higher in the right extremities.

7. The use of a standard blood pressure cuff for both arm and leg in measuring blood pressure seems justified by its simplicity and convenience, in spite of the possible error introduced by the difference in size of the upper and lower extremities.

## REFERENCES


1. Hill, L., Flack, M. and Holtzmann, W. The measurement of systolic blood pressure in man. *Heart*, 1: 73, 1909.
2. Hill, L. and Rowlands, R. A. Systolic blood pressure. (1) In the change of posture. (2) In cases of aortic regurgitation. *Heart*, 3: 219, 1912.
3. Murray, J. R. Systolic and diastolic blood pressures in aortic regurgitation. *Brit. M. J.*, 1: 697, 1914.
4. Williamson, O. K. Comparative systolic blood pressure readings in the arm and leg in aortic incompetence. *Brit. M. J.*, 1: 734, 1921.
5. Bazett, H. C. Factors in the causation of differential blood pressure. *Am. J. Physiol.*, 70: 550, 1924.
6. Burdick, W., Clarke, N., Garlichs, R., Priestly, J. and Richards, D. D. Differences in blood pressure in the arm and leg in normal subjects. *Am. J. Physiol.*, 72: 169, 1925.
7. Strange, J. M. The variations of blood pressure in the extremities. *New England J. Med.*, 200: 167, 1929.
8. Hamilton, W. F., Woodbury, R. A. and Harper, H. T., Jr. Physiologic relationships between intrathoracic, intraspinal and arterial pressures. *J. A. M. A.*, 107: 853, 1936.
9. Cady, J. B. Studies in the vascular physiology of the upper and lower extremities. Univ. Minn. Grad. School Med., 1939. (Quoted by Gambill & Hines.)[11]
10. Wendkos, M. H. and Rossman, P. L. The normal blood pressure in the lower extremity. *Am. Heart J.*, 26: 623, 1943.
11. Gambill, E. E. and Hines, E. A. Blood pressure in the arm and thigh of man. *Am. Heart J.*, 28: 763, 1944.
12. Kotte, J. H., Iglauer, A. and McGuire, J. Measurements of arterial blood pressure in the arm and leg: comparison of sphygmomanometric and direct intra-arterial pressures, with special attention to their relationship in aortic regurgitation. *Am. Heart J.*, 28: 476, 1944.
13. Taussig, A. E. Some blood-pressure phenomena in exophthalmic goiter. *Tr. Ass. Am. Physicians*, 31: 121, 1916.
14. King, J. T. The blood pressure in stenosis at the isthmus (coarctation) of the aorta; case reports. *Ann. Int. Med.*, 10: 1802, 1937.
15. Steele, J. M. Evidence of general distribution of peripheral resistance in coarctation: three cases. *J. Clin. Investigation*, 20: 473, 1941.
16. Stewart, H. J. and Bailey, R. L., Jr. The cardiac output and other measurements of the circulation in coarctation of the aorta. *J. Clin. Investigation*, 20: 145, 1941.
17. Stewart, H. J., Haskell, H. S. and Evans, W. F. The peripheral blood flow and other observations in coarctation of the aorta. *Am. Heart J.*, 28: 217, 1944.
18. Joint Recommendation of the American Heart Association and The Cardiac Society of Great Britain and Ireland: Standardization of Blood Pressure Readings. *Am. Heart J.*, 18: 95, 1939.
19. Amsterdam, B. and Amsterdam, A. L. Disparity in blood pressures in both arms in normals and hypertensives and its clinical significance. *New York State J. Med.*, 43: 2294, 1943.
20. Crafoord, C. and Nylin, G. Congenital coarctation of the aorta and its surgical treatment. *J. Thoracic Surg.*, 14: 347, 1945.
21. Gross, R. E. and Hufnagel, C. A. Coarctation of the aorta; experimental studies regarding its surgical correction. *New England J. Med.*, 233: 287, 1945.

# Relative Importance of Certain Variables in the Clinical Determination of Blood Pressure*

CHARLES E. KOSSMANN, M.D.†
NEW YORK, NEW YORK

THERE are four variables which have an effect on the indirectly determined blood pressure in the brachial artery of man which have been brought to the attention of the clinician in recent years. They are: the position,[2-5] the venous content,[3,4] the thickness,[6] and the location (right or left)[7] of the arm. The importance of these factors does not seem to have been stressed sufficiently, for there is still a clinical tendency to ascribe significance to changes in blood pressure easily attributable to the error of measurement inherent in the sphygmomanometric method. It is the purpose of this paper to reëmphasize these common causes of variance with the method and to add a few observations especially on the relative importance of position and venous content.

## POSITION AND VENOUS CONTENT OF ARM

The effect of position and of venous congestion of the arm was determined by a single examiner making measurements with the same sphygmomanometer in the brachial artery of thirty-two young, stable, healthy male subjects. (Table 1.) This has been done before in a somewhat different way,[2,3,4] but it is believed without giving adequate emphasis to the greater effect of position of the arm. The blood pressures were recorded with the subjects recumbent for five minutes and again after standing for two minutes, observing the details of technic recommended by the American Heart Association.[8] While recumbent the blood pressure was recorded with the subject's arm at his side. Then he was asked to raise it perpendicular to the bed for twenty seconds. At the end of this time the cuff was reinflated, the arm brought back to his side, and blood pressure rapidly recorded. In Figure 1 these two determinations are indicated as "before drainage" and "after drainage" to show that they were taken before and after the arm had been drained of venous blood. With the subject standing for two minutes the blood pressure was taken with the arm pendent at the side. It was raised forward and supported at the level of the heart, taken as 5 cm. below the angle of Louis, and pressure recorded again. Each of these determinations was repeated after draining the arm as indicated above.

Results in Figure 1 and in Table 1 show that although venous drainage does have some effect on the systolic blood pressure with the subject recumbent, and on the diastolic pressure with the subject standing, the position of the arm when the blood pressure is recorded is far more important. Further, with the subject standing with the arm at heart level, venous drainage has little effect, for in this position there is little venous hydrostatic pressure opposing the return flow of blood from the extremity.

* Most of the observations were made at the Army Air Forces School of Aviation Medicine, Randolph Field, Texas.
† From the Department of Medicine, New York University College of Medicine, New York.

TABLE I

| Subject | Age | Ht., Inches | Wt., Lbs. | Blood Pressure, in mm. Hg | | | | | | | | | | | | Circumference of Arm, in cm. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Recumbent 5 min., Arm at Side | | Drain 20 Seconds | Recumbent, Arm at Side | | Standing 2 min., Arm Pendent | | Standing, Arm at Heart Level | | Drain 20 Seconds | Standing, Arm at Heart Level | | Drain 20 Seconds | Standing, Arm Pendent | | 10 cm. above Epicondyles | 10 cm. below Epicondyles |
| B. R. A. | 26 | 69 | 139 | 105 | 71 | | 99 | 71 | 115 | 95 | 95 | 67 | | 105 | 79 | | 109 | 81 | 25 | 26.7 |
| J. A. B. | 20 | 69 | 147 | 118 | 70 | | 126 | 74 | 124 | 84 | 122 | 78 | | 124 | 76 | | 126 | 84 | 26.7 | 25.4 |
| F. L. B. | 21 | 67 | 138 | 114 | 76 | | 108 | 72 | 128 | 100 | 106 | 68 | | 102 | 68 | | 106 | 90 | 26.7 | 26.7 |
| V. P. B. | 24 | 69.5 | 157 | 116 | 74 | | 122 | 68 | 128 | 78 | 118 | 70 | | 114 | 72 | | 120 | 78 | 24.7 | 25.4 |
| M. F. B. | 28 | 65.25 | 147 | 120 | 78 | | 104 | 64 | 110 | 88 | 100 | 60 | | 96 | 62 | | 112 | 78 | 28.6 | 28.6 |
| E. H. B. | 27 | 71 | 170 | 122 | 68 | | 108 | 60 | 110 | 86 | 98 | 60 | | 96 | 56 | | 118 | 78 | 27.2 | 28 |
| G. C. | 25 | 66.75 | 136 | 122 | 72 | | 116 | 70 | 118 | 74 | 112 | 68 | | 106 | 70 | | 110 | 74 | 24.1 | 25.4 |
| M. M. C. | 34 | 71 | 180 | 110 | 78 | | 106 | 74 | 126 | 90 | 114 | 78 | | 106 | 76 | | 118 | 90 | 30 | 30 |
| T. J. F. | 23 | 70.5 | 176 | 120 | 78 | | 118 | 82 | 120 | 100 | 106 | 88 | | 120 | 90 | | 136 | 94 | 27.9 | 26.7 |
| R. R. F. | 32 | 65.25 | 138 | 104 | 52 | | 92 | 58 | 110 | 70 | 86 | 60 | | 88 | 60 | | 110 | 70 | 29.2 | 28 |
| C. R. F. | 23 | 67.5 | 142 | 112 | 78 | | 110 | 78 | 106 | 80 | 102 | 76 | | 102 | 80 | | 108 | 76 | 27 | 26 |
| E. W. G. | 20 | 74.25 | 173 | 144 | 82 | | 138 | 80 | 140 | 100 | 126 | 82 | | 124 | 76 | | 138 | 108 | 28 | 28.6 |
| T. F. H. | 21 | 67 | 147 | 118 | 76 | | 120 | 70 | 118 | 96 | 114 | 90 | | 118 | 84 | | 126 | 90 | 26 | 26 |
| E. J. H. | 22 | 64.5 | 150 | 142 | 88 | | 142 | 88 | 152 | 100 | 140 | 90 | | 136 | 90 | | 150 | 100 | 27.3 | 29.2 |
| H. B. H. | 21 | 71.25 | 155 | 128 | 58 | | 118 | 58 | 126 | 84 | 104 | 62 | | 92 | 58 | | 124 | 74 | 27.2 | 28 |
| R. T. K. | 18 | 64.75 | 113 | 140 | 72 | | 134 | 76 | 128 | 74 | 130 | 70 | | 126 | 68 | | 136 | 78 | 24.1 | 24.7 |
| W. E. L. | 18 | 67.25 | 115 | 128 | 64 | | 118 | 72 | 126 | 92 | 112 | 76 | | 108 | 68 | | 112 | 90 | 23.4 | 24.1 |
| R. L. L. | 21 | 67 | 182 | 132 | 84 | | 126 | 78 | 138 | 90 | 124 | 76 | | 114 | 76 | | 140 | 94 | 29.8 | 29.2 |
| H. S. M. | 23 | 72 | 185 | 120 | 84 | | 108 | 78 | 120 | 94 | 98 | 68 | | 94 | 70 | | 112 | 86 | 31 | 28.6 |
| V. J. M. | 20 | 69 | 157 | 146 | 90 | | 136 | 86 | 150 | 110 | 134 | 100 | | 144 | 88 | | 150 | 98 | 29.8 | 29.8 |
| R. H. P. | 32 | 68 | 136 | 116 | 72 | | 110 | 78 | 110 | 82 | 100 | 72 | | 100 | 64 | | 122 | 82 | 26 | 26 |
| R. C. R. | 22 | 68 | 149 | 122 | 70 | | 120 | 74 | 120 | 100 | 112 | 68 | | 106 | 70 | | 120 | 90 | 28 | 26.7 |
| J. A. R. | 33 | 70 | 143 | 108 | 68 | | 108 | 74 | 104 | 82 | 96 | 64 | | 94 | 74 | | 100 | 76 | 26.7 | 26.7 |
| A. K. R. | 27 | 74.75 | 158 | 124 | 84 | | 132 | 92 | 130 | 98 | 124 | 90 | | 128 | 88 | | 134 | 100 | 26.7 | 27.9 |
| T. H. S. | 22 | 66 | 140 | 98 | 68 | | 102 | 68 | 106 | 78 | 84 | 66 | | 96 | 64 | | 102 | 74 | 26.7 | 26.7 |
| O. E. S. | 22 | 68.75 | 136 | 120 | 80 | | 118 | 70 | 130 | 100 | 110 | 70 | | 102 | 68 | | 130 | 96 | 25.4 | 27.3 |
| R. E. S. | 25 | 69 | 160 | 120 | 76 | | 116 | 76 | 114 | 76 | 108 | 76 | | 88 | 60 | | 112 | 76 | 30.5 | 29.2 |
| E. C. T. | 31 | 71.5 | 193 | 124 | 78 | | 118 | 80 | 130 | 94 | 112 | 84 | | 100 | 84 | | 124 | 90 | 29.8 | 28.6 |
| J. H. T. | 21 | 69.25 | 139 | 120 | 80 | | 110 | 74 | 110 | 90 | 100 | 72 | | 96 | 70 | | 124 | 88 | 25.4 | 26.7 |
| F. P. V. | 24 | 69.5 | 153 | 122 | 80 | | 122 | 72 | 126 | 100 | 116 | 78 | | 118 | 78 | | 144 | 96 | 27.9 | 27.9 |
| P. F. W. | 21 | 67 | 143 | 108 | 66 | | 106 | 62 | 106 | 74 | 80 | 64 | | 94 | 56 | | 96 | 74 | 26 | 25.4 |
| W. J. W. | 21 | 68 | 166 | 150 | 80 | | 146 | 90 | 150 | 90 | 146 | 88 | | 138 | 94 | | 150 | 90 | 27.5 | 28 |
| Mean: | 24.0 | 68.7 | 152.0 | 121.7 | 74.8 | | 117.4 | 74.0 | 122.8 | 89.0 | 110.3 | 74.3 | | 108.6 | 73.0 | | 124.3 | 85.7 | 27.2 | 27.3 |
| Standard Deviation: | 4.3 | 2.5 | 18.5 | 12.2 | 8.1 | | 12.6 | 8.3 | 13.0 | 10.0 | 15.2 | 10.2 | | 14.9 | 10.3 | | 18.4 | 9.5 | 1.9 | 1.5 |
| S. E. of Mean: | .78 | .45 | 3.32 | 2.19 | 1.45 | | 2.26 | 1.50 | 2.33 | 1.80 | 2.73 | 1.83 | | 2.68 | 1.86 | | 3.31 | 1.71 | .35 | .27 |

The most obvious reason for the importance of the position of the arm in determining levels of blood pressure would appear to be the hydrostatic column of blood in the brachial artery between the level of the heart and the level of recording blood pressure in the arm. In order to estimate how much effect a column of blood in the brachial artery will have on the blood pressure, the distance from the level of the heart (5 cm. below the angle of Louis) to the antecubital fossa of the pendent arm was measured in twenty subjects and found to average 20.68 cm. In these same twenty subjects the average systolic pressure in the pendent right arm was 115.9 mm. Hg and the diastolic was 87.3 mm. Hg. By elevating the arm to the level of the heart, these values fell to 105.8 and 74.9 mm. Hg, respectively. The average fall of the two considered together was 11.3 mm. Hg. If this value in mercury is converted to blood, it is equivalent to 14.6 cm. In this series, then, the change in blood pressure was about one-third less than expected on the basis only of hydrostatics. This statement assumes that the Korotkoff sounds are determined by pressure in that part of the vessel over which they are heard.

Regardless of cause, the significance of these few observations is that one of the most important variables concerned with

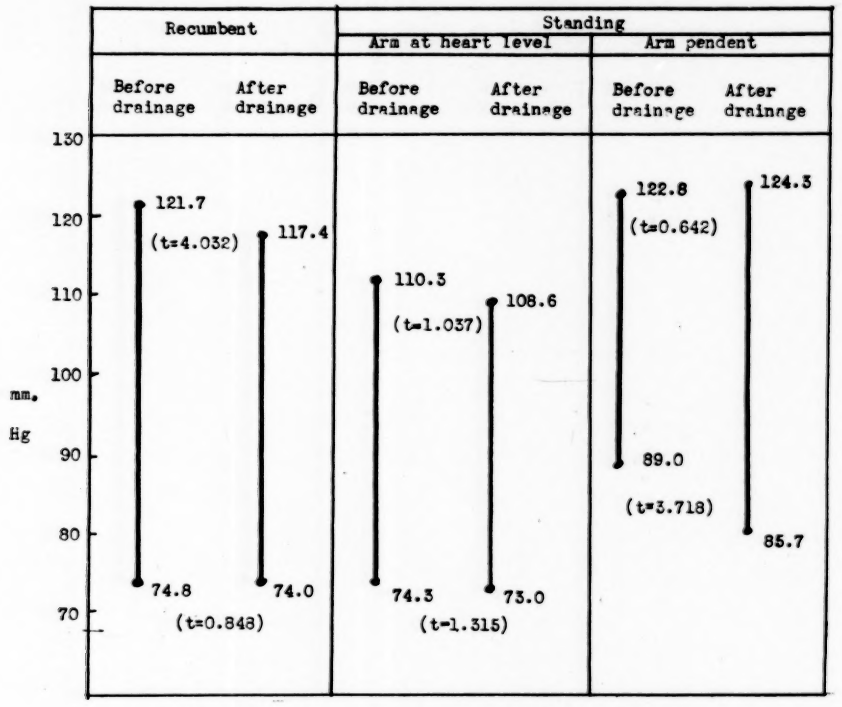



FIG. 1. Mean blood pressures in thirty-two normal subjects.

$$t = \frac{\text{mean difference}}{\text{S. E. of mean differences}}$$

The mean difference is highly significant ($P < 1\%$) if the value of $t$ is greater than 2.75.

the level of blood pressure determined clinically is the position of the arm, and venous congestion is of significance largely as it is caused by this position. As recommended by the American Heart Association,[8] the arm should always be at the level of the heart (5 cm. below the sternal angle) when recording blood pressures, whatever the posture of the subject may be.

### THICKNESS OF THE ARM

On comparing directly determined blood pressure with sphygmomanometric measurements, it has been ascertained that in general the thicker the arm the higher the blood pressure, particularly the systolic pressure.[6] The importance of this variable was tested further by comparing the thickness of the extended arm 10 cm. above and 10 cm. below the humeral epicondyles with the blood pressure recorded by one observer in the same arm of thirty-two normal subjects in the recumbent position. (Table II.) There was little correlation between the systolic blood pressure and the circumference of the arm at either level. However, there was a fair correlation between the diastolic blood pressure and the circumference of the arm 10 cm. above the epicondyles (coefficient of correlation 0.310), and a good correlation

TABLE II
CORRELATIONS OF BLOOD PRESSURE AND CIRCUMFERENCE OF ARM

| | *Systolic* Blood Pressure, Subject Recumbent 5 Minutes | | *Diastolic* Blood Pressure, Subject Recumbent 5 Minutes | |
|---|---|---|---|---|
| | With Circumference of Arm 10 cm. *above* Epicondyles | With Circumference of Arm 10 cm. *below* Epicondyles | With Circumference of Arm 10 cm. *above* Epicondyles | With Circumference of Arm 10 cm. *below* Epicondyles |
| Coefficient of Correlation | .092 | .281 | .310 | .463 |

between the diastolic blood pressure and the circumference of the arm 10 cm. below the epicondyles (coefficient of correlation 0.463). Little can be done to control this particular variable in measuring the blood pressure clinically by the sphygmomanometric method, although clearly the patient with muscular or fat arms is at a disadvantage when rigid criteria of normal blood pressure are utilized.

## RIGHT OR LEFT ARM

No experiments were done on the sphygmomanometric measurement of arterial pressure simultaneously in the two arms. However, available data[7] indicate that the difference in normal subjects is of sufficient size and frequency to make it obligatory to make comparative measurements in the same arm.

## SUMMARY AND CONCLUSIONS

1. Blood pressure should always be determined without any part of the arm below the level of the heart (5 cm. below the sternal angle) regardless of the position of the subject.

2. When blood pressure is determined with the arm at heart level the average effect of draining the arm of venous blood is negligible.

3. There is a good positive correlation between thickness of the arm 10 cm. below the epicondylar line and the level of the diastolic blood pressure. The examinee with thick forearms is at a disadvantage when rigid criteria of normal blood pressure are used.

4. From data available elsewhere, it is obligatory to make all comparative determinations on the same arm.

## REFERENCES

1. Kossmann, C. E. Some observations on blood pressure relative to the examination for flying. AAF School of Aviation Medicine Project 264, Report 2, March 31, 1945.
2. Kahn, M. H. The position of the arm in blood pressure measurements. *Am. J. M. Sc.*, 158: 823–829, 1919.
3. Berry, M. R., Jr. The influence of the position of arm and body on blood pressure determined by auscultation. *Proc. Staff Meet., Mayo Clin.*, 16: 29–32, 1941.
4. Berry, M. R., Jr., Horton, B. T. and MacLean, A. R. The importance of studying the postural responses of the blood pressure and the heart rate, with a note on the method of taking blood pressure in the erect posture. *M. Clin. North America*, 24: 1095–1126, 1940.
5. Stein, I. The effect of changes of position of the arm upon the blood pressure. *Am. Heart J.*, 31: 477, 1946.
6. Ragan, C. and Bordely III, J. The accuracy of clinical measurements of arterial blood pressure. *Bull. Johns Hopkins Hosp.*, 69: 504–528, 1941.
7. Southby, R. Some clinical observations on blood pressure and their practical application, with special reference to variation of blood pressure readings in two arms. *M. J. Australia*, 22: 569–580, 1935.
8. Committee for Standardization of Blood Pressure Readings of the American Heart Association and of the Cardiac Society of Great Britain and Ireland: Standard method for taking and recording blood pressure readings. *J. A. M. A.*, 113: 294–297, 1939.

# Concentration of Renin in Renal Venous Blood in Patients with Chronic Heart Failure*

ARTHUR J. MERRILL, M.D., JAS. L. MORRISON, PH.D. *and* EMMETT S. BRANNON, M.D.

ATLANTA, GEORGIA

THE renal blood flow in patients with congestive heart failure is greatly reduced.[1,2] It has been shown experimentally that renal ischemia stimulates production of a substance called renin, which causes vasoconstriction.[3] It is, therefore, logical to wonder if renin production is increased in patients with cardiac failure. The clinician finds certain phenomena which indicate that active vasoconstriction does occur in heart failure, i.e., the maintenance of normal or increased blood pressure in the presence of a falling cardiac output; the rapid rise in venous pressure in acute heart failure and pericardial tamponade without increase in blood volume;[4] the early fall in venous pressure without decrease in blood volume and the fall in peripheral resistance which occur when the circulation improves in response to digitalis.[5] In severe heart failure we have found a reduction in renal blood flow out of proportion to the reduction in cardiac output.[2] The renal blood flow was reduced to a much greater degree than the filtration rate, suggesting a high filtration pressure. This points to intrinsic renal vasoconstriction, most likely of the efferent arterioles which could be produced by renin.[6,7] These considerations have led to the investigation of renin production in heart failure.

## METHOD

The concentration of renin is determined by a biological assay in which there are many sources of error. Any vasoconstrictor substance formed in the kidney and discharged into the blood stream is greatly diluted by the time blood is collected from the usual site at the elbow. It was obviously desirable to avoid this dilution by obtaining blood directly from the renal vein. This was done by the technic previously described from this laboratory.[8] A flexible radiopaque catheter was introduced into the venous system through the antecubital vein. Under fluoroscopic control this was threaded through the superior vena cava, right atrium and inferior vena cava into the renal vein. In order to be certain that the catheter was in the renal vein a solution of sodium para amino hippurate* was injected and samples of blood analyzed from the femoral artery and from the catheter. The finding that the hippurate had been extracted as the blood passed through the kidney demonstrated that the catheter was actually in the renal vein. The renin content of blood from the renal vein was compared with that of blood collected simultaneously from the femoral

* Sodium para amino hippurate was obtained through the courtesy of Sharpe and Dohme.

* From the Departments of Medicine and Pharmacology, Emory University School of Medicine, and the Medical Service of Grady Hospital, Atlanta, Georgia. This work was made possible by a grant from Smith, Kline and French Laboratories.

artery. The use of arterial blood as a control eliminated the presence of vasoconstrictor substances which might have been present from sources other than the kidney or which might have been formed in the blood during the assay. Dogs were used for the assay because they are relatively insensitive to renin and would not be expected to show positive results unless significant amounts were present. Samples of blood from normal subjects and from those with congestive failure were assayed without the observer knowing the source of the samples.

The blood was citrated and iced immediately, then centrifuged as quickly as possible at room temperature. The plasma was separated and frozen with dry ice. It was kept in this state until bioassays could be made conveniently.

The plasma was prepared by the technic of Haynes and Dexter[9] and the concentrate from 10 cc. of dialysate injected intravenously into dogs anesthetized with sodium pentobarbital (30 mg./K.). Blood pressure rises were recorded graphically through a cannula placed in the carotid artery. Frequent intermediate injections of angiotonin were given, calculated to produce a standard rise of 20 to 35 mm. Hg in the test animals. Since dogs are approximately one-fourth as sensitive to renin as cats, four times as much angiotonin was used in our dogs as is used in cats. The number of dog units was determined from the formula:

$$X = \left(\frac{Y}{St}\right)^2$$

X = number of dog units
Y = rise in blood pressure produced by the unknown
St = rise in blood pressure produced by the standard

## RESULTS

*Normal Subjects.* Renin assays were carried out on renal venous blood and arterial blood from five normal subjects. No renin was detected in either the renal venous or arterial bloods. Renal venous blood from normal subjects has been found by Dexter[10] and Page, E. W.[11] to contain small amounts of renin in about half the cases. Cats used by Dexter are about four times as sensitive to renin as dogs used in our experiments. Page used the rat uterus. It is likely that we should have found small amounts in the renal venous blood if we had used more sensitive animals.

TABLE I
OBSERVATIONS IN ELEVEN PATIENTS IN CHRONIC CONGESTIVE FAILURE

| Patient | Renal Plasma Flow | Filtration Rate | Filtration Fraction | Units of Renin in Renal Venous Blood | B. P. Rise in Dog | Arteriovenous $O_2$ Difference | |
|---|---|---|---|---|---|---|---|
| | Cc. per 1.73 sq. m. per mm. | Cc. per 1.73 sq. m. per mm. | | | Mm. Hg | Systemic | Renal |
| J. C. | 91 | 37 | 40.6 | .56 | 24 | 7.9 | 4.4 |
| L. H. | 177 | 64 | 36.2 | 1.14 | 28 | 6.8 | 4.4 |
| L. F. | 248 | 57 | 23.0 | .49 | 18 | 6.3 | 2.5 |
| L. H. | 157 | 70 | 44.6 | .25 | 10 | 6.3 | 3.8 |
| W. L. | 272 | 93 | 34.6 | .00 | 0 | 5.2 | 2.4 |
| S. H. | 174 | 72 | 41.0 | .36 | 20 | 5.0 | 4.0 |
| J. M. | ... | .. | .... | .28 | 16 | 5.1 | 2.5 |
| J. McW. | 269 | 84 | 31.4 | .39 | 24 | 4.9 | 2.8 |
| C. McM. | 326 | 131 | 40.2 | .54 | 22 | ... | ... |
| L. V. E. | 264 | 99 | 37.5 | .00 | 0 | 5.9 | 2.8 |
| M. L. K. | 332 | 96 | 29.0 | .00 | 0 | 5.2 | 2.8 |

*Patients with Congestive Failure.* Observations were made on eleven patients with heart failure. The renal blood flow was reduced in all. No renin was found in any of the samples of arterial blood, but it was detected in significant amounts in eight of the eleven patients with heart failure. (Table I.) There was no definite correlation between the amounts found and the renal blood flow, but the technic used is too crude to be considered quantitative.

Why three of the samples of blood from the renal vein did not contain sufficient renin to be detected by the technic used was not determined. It may be that the renal blood actually contained little renin. It is possible that some blood was aspirated from the vena cava or that the tip of the catheter lay near the mouth of a vein entering the renal vein from some other organ than the kidney or that the dog as an experimental animal is too insensitive to respond to smaller concentrations of renin.

## COMMENTS

These observations demonstrate that renin is present in a high concentration in the renal blood in the majority of patients with severe congestive failure. This finding further confirms the observations of Merrill[2] that the renal blood flow in patients with severe congestive failure frequently falls to a level as low as one-fifth of the normal value. Renal venous blood in these patients should afford a potent source of human renin for experimental studies.

From the data reported here it is not possible to compare quantitatively the production of renin in patients with chronic failure with that in normal subjects. The renal blood flow in patients with chronic failure was one-third to one-fifth that present in the normal subjects. If the production of renin by the kidney was the same in both groups of subjects, it would be more concentrated in those with the slow blood flow.

There is considerable evidence that vasoconstriction occurs in heart failure. The cardiac output falls to a greater extent than does the arterial pressure. This finding is indicative of arteriolar constriction. The renal blood flow is greatly reduced and the high filtration fraction suggests that efferent constriction is greater than afferent constriction.[6]

Part of the changes in venous pressure seems to result from vasoconstriction. The rise in venous pressure seen in patients with congestive heart failure seems best explained by two mechanisms, increase in blood volume and increase in vasoconstrictor tone. Warren and Stead showed that in patients with fixed chronic heart failure the venous pressure varies with the blood volume.[12] In patients with acute pericardial tamponade, relief of the tamponade causes an immediate fall in venous pressure which is not caused by a change in blood volume.[13] In patients in whom the administration of digitalis causes the circulation to improve, an early fall in venous pressure occurs which is not the result of a decrease in blood volume.[5] These changes in venous pressure seem best explained by a redistribution of blood within the vascular bed as a result of changes in tone of the vascular system.

At least three of these manifestations of congestive heart failure, i.e., well maintained peripheral resistance in the presence of a decrease in cardiac output, decreased renal blood flow out of proportion to fall in cardiac output and production of renin, also occur in acute hemorrhage.[14,15,16] They are probably a manifestation of the reduced cardiac output itself. At first glance one is surprised to find such a striking similarity between the dynamics of acute hemorrhage and congestive failure as these conditions present very different clinical pictures. In hemorrhage the venous pressure is low; in heart failure, high. This difference does not necessarily mean that vasoconstriction has not occurred in both conditions. In the patient with hemorrhage, the blood volume has simply fallen so low that vasoconstriction cannot maintain a normal pressure. In heart failure the same degree of vasoconstriction with a normal blood volume will produce an elevated venous pressure. If the heart failure is of some duration and

the blood volume is increased, an even more striking rise in venous pressure may occur. These relationships between blood volume and venous pressure have been recorded elsewhere.[13]

The edema so characteristic of heart failure is absent in patients with acute hemorrhage, but in both groups of patients oliguria is the rule. The patient with acute hemorrhage either recovers or dies in a relatively short time. If he should survive with an inadequate circulation and oliguria, edema would form if given sufficient salt and water over a long enough time.

The fact that renin is produced by the kidneys in congestive failure and that generalized vasoconstriction occurs does not necessarily mean that the renin produces the vasoconstriction. From the data at hand two explanations are equally possible. Vasoconstriction in the kidney may occur from reflex stimulation when the cardiac output falls. The fall in renal blood flow from reflex vasoconstriction then may stimulate the production of renin which may or may not be responsible for some of the other vasoconstrictor phenomena observed. On the other hand, the fall in blood flow in all organs might be equal when the cardiac output becomes inadequate. The fall in blood flow through the kidney might then stimulate renin production which might cause active vasoconstriction in the kidney and other organs.

These observations on the increased renin concentration of renal venous blood in patients with congestive heart failure offer a new approach to the study of some of the clinical phenomena observed in heart failure. They stimulate our interest in the mechanisms by which the venous pressure becomes high in congestive heart failure and make us conscious of the need for further investigation of the mechanism causing renal vasoconstriction when the cardiac output is inadequate.



SUMMARY

1. Renal venous blood was obtained from five normal subjects and eleven patients with fixed chronic congestive failure. A catheter introduced into the antecubital vein was threaded through the venous system into the renal vein. Dogs were used for the assay of renin.

2. No renin was detected in the renal venous blood or arterial blood of the normal subjects. It is to be noted that the dog is only about one-fourth as sensitive to renin as the cat.

3. Significant amounts of renin were found in the renal venous blood of eight of the eleven patients with chronic heart failure. No renin was detected in the arterial blood.

4. The finding of increased concentration of renin in the renal venous blood of patients with chronic congestive failure is additional evidence in support of the finding that the renal blood flow is greatly reduced in chronic heart failure.

5. The well maintained blood pressure in the presence of a low cardiac output, the sudden changes in venous pressure produced by relieving pericardial tamponade and by improvement of the circulation by digitalis, and the marked fall in renal blood flow out of proportion to the fall in cardiac output all suggest that active vasoconstriction is present in patients with heart failure. No final conclusion can be reached at this time as to whether renin is responsible for some of the observed vasoconstriction.*

REFERENCES

1. Seymour, William B., Pritchard, Walter H., Longley, L. P. and Hayman, J. M., Jr. Cardiac output, blood and interstitial fluid volumes, total circulating serum protein and kidney function during cardiac failure and after improvement. *J. Clin. Investigation*, 21: 229, 1942.

2. Merrill, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart

* The hypertensin used for renin standardization was furnished through the courtesy of Dr. K. G. Kohlstaedt, of the Lilly Research Laboratory.

failure: evidence of "forward failure" as the primary cause of edema. *J. Clin. Investigation*, 25: 398, 1946.

3. Goldblatt, H. Studies on experimental hypertension; the pathogenesis of experimental hypertension due to renal ischemia. *Ann. Int. Med.*, 11: 69, 1937.
4. Cooper, F. W., Stead, E. A., Jr. and Warren, J. V. The beneficial effects of intravenous infusions in pericardial tamponade. *Ann. Surg.*, 120: 822, 1944.
5. Unpublished data from this laboratory.
6. Smith, H. W. Lectures on the Kidney. University Extension Division, University of Kansas, Lawrence, Kansas. P. 51. 1943.
7. Merrill, A. J., Williams, J. R. and Harrison, T. R. The site of action of the renal pressor substance. *Am. J. M. Sc.*, 18: 196, 1938.
8. Warren, J. V., Brannon, E. S. and Merrill, A. J. Method of obtaining renal venous blood in unanesthetized persons, with observations on extraction of oxygen and sodium para-amino-hippurate. *Science*, 100: 108, 1944.
9. Haynes, Florence and Dexter, Lewis. Personal communication.
10. Dexter, Lewis. Personal communication.
11. Page, Ernest W. Personal communication.
12. Warren, J. V. and Stead, E. A., Jr. Fluid dynamics in chronic congestive heart failure. *Arch. Int. Med.*, 73: 138, 1944.
13. Warren, J. V., Brannon, E. S., Stead, E. A., Jr. and Merrill, A. J. Pericardial tamponade from stab wound of the heart and pericardial effusion or empyema: a study utilizing the method of right heart catheterization. *Am. Heart J.*, 31: 418, 1946.
14. Brannon, E. S., Stead, E. A., Jr., Warren, J. V. and Merrill, A. J. Hemodynamics of acute hemorrhage in man. *Am. Heart J.*, 31: 407, 1946.
15. Lauson, Henry D., Bradley, Stanley E. and Cournand, Andre. The renal circulation in shock. *J. Clin Investigation*, 23: 381, 1944.
16. Dexter, Lewis, Frank, H. A., Haynes, F. W. and Altschule, M. D. Traumatic shock. IV. The effect of hemorrhagic shock on the concentration of renin and hypertensinogen in the plasma in unanesthetized dogs. *J. Clin. Investigation*, 22: 827, 1943.

# Relief of Pellagrous Glossitis with Synthetic Folic Acid*

TOM D. SPIES, M.D.
BIRMINGHAM, ALABAMA

OUR working hypothesis in the study of nutritive failure during the past fifteen years may be stated briefly as follows: Impoverished cells have many disturbances operating in their biochemical systems simultaneously. If the nutrients necessary to correct these disturbances are not supplied, the derangement becomes more and more widespread. Each specific corrective measure applied would tend to lead toward normal. Almost full nutritive restoration, however, can come only after long continued administration of all the needed essential substances. In studying pellagra and associated deficiencies, we have placed particular emphasis on the interrelationship between the clinical manifestations of the various syndromes. A certain relative degree of specificity has been studied by ourselves and by others. Frequently, we have seen the administration of a nutrient specific for a single deficiency not only correct that deficiency but cause considerable general improvement in the patient.

Early in my studies on the interrelationship between pellagra and certain macrocytic anemias frequently found in pellagrins, I found that very large doses of ventriculin, liver or liver extract were beneficial in relieving the pellagrin but that the small amounts of liver extract which will produce a remission in Addisonian pernicious anemia in relapse were insufficient to relieve the signs and symptoms of severe pellagra. Later I noted that niacin, which is effective in relieving pellagrous glossitis, dermatitis and the gastrointestinal disturbances of pellagra, did not correct the associated macrocytic anemias. For a number of years I have thought that vitamins and enzymes should work through certain biochemical systems in the body and that a considerable number of chemical substances might affect these biochemical systems in such a way as to produce a satisfactory therapeutic result. The present communication is concerned with the remission of macrocytic anemia and of pellagrous glossitis in two persons following the administration of synthetic folic acid.

## CASE REPORTS

CASE 1. J. S., a sixty-three-year-old white man, had been under observation in the Nutrition Clinic from 1939 to 1946. When he was first seen, a diagnosis of nutritional macrocytic anemia and pellagra was made. His initial red blood cell count was one million and his initial hemoglobin content was 32 per cent. He had free hydrochloric acid, pepsinogen and rennin in the gastric contents after histamine stimulation. The bone marrow showed typical megaloblastic arrest. He had extensive pellagrous dermatitis on the dorsum of the hands, on the dorsum of the wrists and on the lower part of the forearms. His tongue showed isolated, clear-cut and well demarcated areas of pellagrous glossitis. His dietary history revealed that for many years he

* From the Department of Internal Medicine, University of Cincinnati School of Medicine; University of Cincinnati Studies in Nutrition at the Hillman Hospital, Birmingham, Alabama. The expenses of this study were borne by grants from Lederle Laboratories, Inc. and Ingalls Foundation.

had existed on an inadequate diet and that he did not eat lean meats. After all baseline determinations were made, he was given daily injections of liver extract, and on the fifth day he experienced a great increase in strength and a feeling of well being. Three days later the reticulocytes peaked at 30 per cent. This response was followed by an increase in red blood cells and hemoglobin. After the former had reached a count of three million, he was allowed to go home with the understanding that he would return. At the time of his discharge, the pellagrous glossitis and dermatitis were essentially unchanged. He felt so much better that he did not wish any more treatment of any kind.

He was visited frequently in his home for observation. Five months after he was discharged, the pellagrous dermatitis and glossitis became much more severe, and his anemia had relapsed and he came to the hospital. He was given a single oral dose of 300 mg. of niacinamide, and within twenty-four hours his tongue was objectively and subjectively normal. Two days later the erythematous border of the pellagrous dermatitis began to fade. His blood values remained unchanged. Daily injections of liver extract were followed by prompt blood regeneration. During the next four years he had several relapses of pellagra and of the anemia. On his last admission in 1945 he was given intramuscularly 0.5 cc. of reticulogen for ten days. He had a prompt and characteristic remission of his anemia, but there was no apparent change in the pellagrous dermatitis or glossitis which was again present on this admission. With all the treatments he had had to relieve his pellagrous glossitis and dermatitis (300 to 500 mg. nicotinic acid daily on four other occasions), in no instance did detectable blood regeneration follow the administration of nicotinic acid.

In the spring of 1946 he again had a remission of the anemia and a recurrence of the pellagrous glossitis. (Fig. 1.) This time he was given a daily oral dose of 10 mg. synthetic Lactobacillus casei factor after all baseline determinations had been made. Two days later the burning of the tongue disappeared and it appeared less red. By the fifth day there was evidence of a great degree of healing of the tongue. (Fig. 3.) The reticulocytes peaked at 19 per cent on the seventh day and an increase in red blood cells followed in the usual way.[1]

Case II. B. B., a fifty-five-year-old Negro woman, was admitted to the Nutrition Clinic in 1942 with a diagnosis of Addisonian pernicious anemia and pellagra. Her red blood cell count was 1.7 million and her hemoglobin was 49 per cent. She had no free hydrochloric acid, pepsinogen or rennin in the gastric contents after histamine injection. The bone marrow showed megaloblastic arrest. She had four areas of pellagrous glossitis characterized by being well demarcated, very red and very sore. Areas of pellagrous dermatitis covered both elbows. Her dietary history showed that for the past ten years she had been eating carbohydrates preponderantly. The administration of 0.5 cc. of reticulogen intramuscularly each day for ten days was followed by a characteristic remission of the anemia, but there was no apparent change in the pellagrous glossitis or the dermatitis. She was discharged with her red blood cell level at three million, but she did not wish to report back for additional therapy. She was seen frequently in her home.

Since the pellagrous glossitis persisted, she was given 500 mg. of niacinamide by mouth each day for four days and it healed completely. The red blood count and hemoglobin, which were beginning to fall, were not affected by the administration of niacinamide. During the next four years she had three relapses of pellagra and two of anemia. Each time liver extract relieved the anemia and the niacinamide relieved the pellagrous glossitis. In February, 1946, she had a relapse of the anemia and a recurrence of the pellagrous glossitis. She was admitted to the hospital, baseline determinations were made, and 10 mg. of synthetic Lactobacillus casei factor was administered daily by mouth. On the second day she volunteered that her tongue no longer burned. On the fifth day it was subjectively and objectively normal. By this time reticulocyte regeneration had begun. It reached a peak of 16.6 per cent on the seventh day and was followed by a prompt increase in red blood cells and hemoglobin.

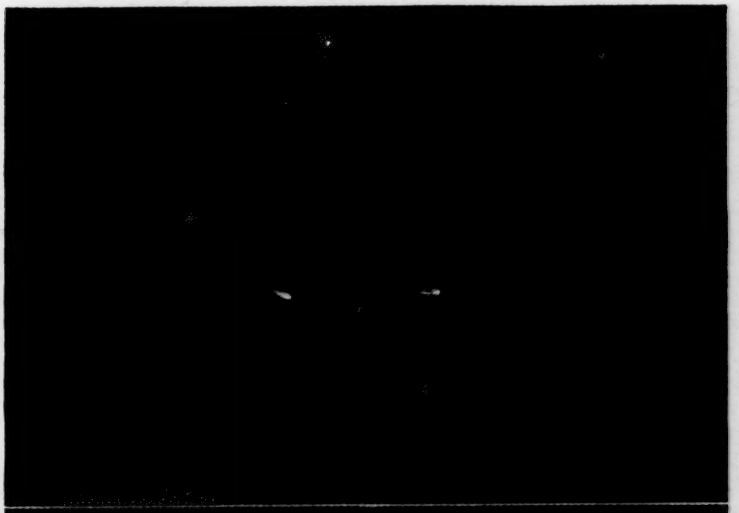


FIG. 1. Photograph of recurrent pellagrous glossitis in Case 1. Note the swelling and erythema in isolated areas of the tongue.

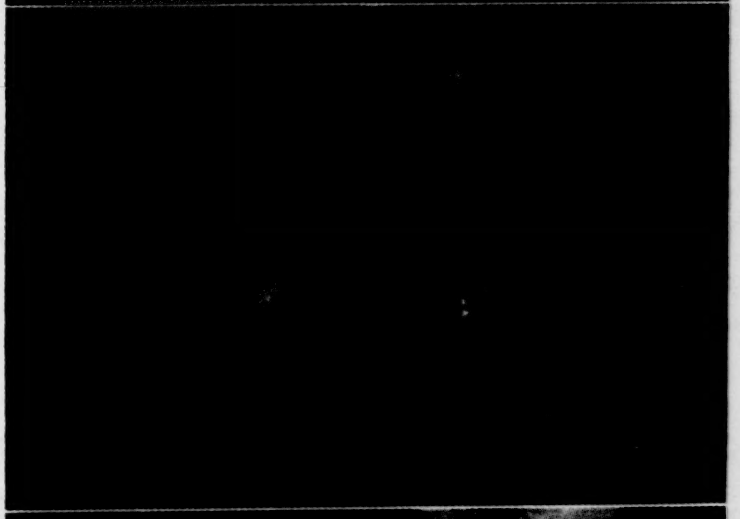


FIG. 2. Photograph of same patient taken on the fourth day after patient had received 10 mg. folic acid daily. The tongue is less swollen and the areas of pellagrous glossitis are less red.

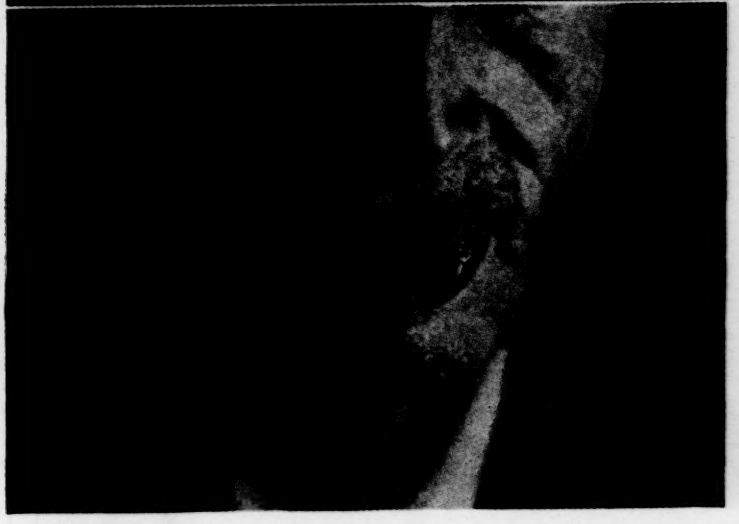


FIG. 3. Photograph of same patient on the fifth day of therapy. The tongue is grayish and the pellagrous glossitis has almost disappeared. One small area of residual change which is still evident disappeared the next day.

## SUMMARY AND CONCLUSIONS

Following the administration of synthetic folic acid to two patients with macrocytic anemia in relapse and pellagrous glossitis, there was prompt regeneration of the blood and profound improvement in the glossitis. In both cases several relapses of the anemia had responded to liver extract and the pellagrous glossitis had disappeared following the administration of niacinamide. On no occasion, however, did the glossitis respond to the small doses of liver extract employed nor did any hemopoietic response occur following niacinamide therapy. We previously had observed that great improvement of the entire alimentary tract occurred in persons with sprue following the administration of folic acid and that persons with pernicious anemia and nutritional macrocytic anemia likewise had subjective and objective improvement of their glossitis. Up until the present time, however, synthetic folic acid is the only single chemical substance we have found that is effective in treating both macrocytic anemia and pellagrous glossitis in these two patients.

These observations will result in some unavoidable confusion since clinical medicine has not grown up as an exact science. Such clinical syndromes will not be entirely explained until we understand human nutrition and nutritional deficiency diseases with all that this implies about the interrelationship of the various nutrients and the overlapping of some of their functions. The clinical improvement described in these patients following a short course of therapy is temporary; and from a practical, therapeutic point of view I recommend that the physician treating similar cases give suitable antianemic therapy and administer a mixture of indicated vitamins and a diet high in proteins for as long as necessary. The author considers niacinamide, not folic acid, as a specific therapeutic agent for the pellagrin. Yet it is well for the physician to realize that each nutrient may well have some specificity and also have a profound and general function in our bodies. Our observations in the two cases reported give support to our working hypothesis that in persons with mixed deficiency diseases there are definite alterations in the biochemical systems which can be corrected by proper therapy.


## REFERENCE


1. Spies, Tom D. Folic acid for macrocytic anemia in relapse. *J. A. M. A.*, 130: 474–477, 1946.

# Results from Subtotal Gastric Resection in Peptic Ulcer*

## *The Internist's Viewpoint*

T. Grier Miller, M.D. *and* Joseph T. L. Nicholson, M.D.
PHILADELPHIA, PENNSYLVANIA

Various procedures are now available for the management of the patient with a benign peptic ulcer who does not readily recover and remain well on an ordinary dietary and hygienic regimen. Irrespective of the reason for the persistence of the lesion, whether it be a constitutional gastric hyperacidity, some psychogenic factor, an inability or failure on the part of the patient to observe directions or the development of one of the recognized ulcer complications, some additional therapeutic measure is then indicated. This may be a prolonged period of hospitalization with twenty-four-hour neutralization of the gastric acidity, radiotherapy, hormone therapy, the administration of amino acids or some operative undertaking. Obviously, for the patient with an irreversible pyloric obstruction, or, in the instance of a gastric lesion with some doubt as to the benignancy of the ulcer, surgery alone need be considered. In these situations, however, as well as in all the other complications, with the possible exception of perforation, the internist or gastro-enterologist is usually called upon to make the decision regarding the type of therapy that will give the patient his best chance of permanent and satisfactory cure.

In an attempt to clarify the indications for surgical interference and especially to show, for subsequent comparison with other procedures, the probable results from subtotal gastrectomy, we present in this publication a report on our experience with that operation over an eight-year period. The series does not represent the total experience of our surgeons, or our own total experience, with gastric resection. It includes only the cases that have been studied preoperatively and postoperatively by the senior author in his private office and in the out-patient gastrointestinal section and the wards of the medical clinic of this hospital; also, only those that we have been able to follow to date. It does, however, include, in addition to the so-called refractory cases, all those patients who were operated upon for repeated hemorrhage, for pyloric stenosis and for roentgen evidence of deep penetration or perforation of the gastric, duodenal or jejunal wall, but none that subsequently was proved to be malignant.

### SUBJECTS AND DATA

The data are from 113 cases, all operated upon from October, 1938, through 1945; only three, otherwise acceptable, have been eliminated because they could not be followed either by personal interview or correspondence. Earlier cases have not been included, because before 1938 extensive gastric resection was not frequently employed for peptic ulcer in this hospital. Since then a subtotal gastrectomy with an antecolic Balfour or Hofmeister end-to-side gastro-

* From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pa.

jejunostomy has been the usual operative procedure.

Obviously, many of the cases have been followed for only one or a few years, but it will be noted below that up to, and even beyond, five years the results of the follow-up period for each year were approximately the same.

As cured we have included only those patients with no residual digestive symptoms; as improved, those that have been relieved of their previous symptoms of ulcer type, but still have vague digestive symptoms of the sort often encountered in patients without demonstrable organic disease of the digestive tract; and as unimproved, those that have continued to present symptoms or roentgenological evidence of ulcer or of one of its complications. These latter must be regarded as surgical failures, and to them special attention will be directed. We have also listed in our tables, for their effect on the statistical results, those that have died, either from the operation itself or subsequently from some complication.

TABLE I
AGE AND SEX IN 113 PATIENTS WITH PEPTIC ULCER SUBJECTED TO GASTRIC RESECTION

| Age in Decades | Male | Female | Total |
|---|---|---|---|
| 20–29 | 6 | 3 | 9 |
| 30–39 | 12 | 6 | 18 |
| 40–49 | 18 | 6 | 24 |
| 50–59 | 35 | 8 | 43 |
| 60–69 | 14 | 2 | 16 |
| 70–79 | 3 | 0 | 3 |
| Totals | 88 | 25 | 113 |

Table I shows the sex and age of the 113 patients at the time of operation. Eighty-eight, or 78 per cent of them, were of the male sex and the largest number, 43, or 38 per cent, were in the sixth decade of life. More than a half of the total number, 59 per cent, were in the fifth and sixth decades. It is particularly interesting that three were in the eighth decade; one of these was seventy-nine years old and today is active and well at eighty-two.

Table II indicates that in twenty-four of the cases the ulcerative lesion was gastric in location; in seventy-three duodenal; in ten both gastric and duodenal, and in six gastrojejunal or marginal (secondary to previous gastro-enterostomy). It also shows that of the total, forty-two were resected because of the refractory nature of the ulcer (not satisfactorily responsive to the medical regimen); twenty-three because of recurrent hemorrhage, and nineteen because of pyloric stenosis; while in sixteen a malignant lesion could not otherwise be eliminated with certainty, and in thirteen deep penetration of the wall either had been demonstrated by roentgen ray studies or was suspected clinically. In two of the latter cases subacute perforation had occurred.

TABLE II
INDICATION FOR GASTRIC RESECTION IN 113 PATIENTS WITH PEPTIC ULCER

| Indication for Operation | Location of Lesion | | | | |
|---|---|---|---|---|---|
| | Gastric | Duodenal | Gastric and Duodenal | Marginal | Total |
| Refractory to medical therapy | 5 | 33 | 2 | 2 | 42 |
| Recurrent hemorrhage | 3 | 15 | 2 | 3 | 23 |
| Stenosis | 3 | 13 | 2 | 1 | 19 |
| Possible malignant degeneration | 10 | 3 | 3 | 0 | 16 |
| Deep penetration | 3 | 9 | 1 | 0 | 13 |
| Totals | 24 | 73 | 10 | 6 | 113 |

Table III shows the results obtained from the resection for each location of the ulcer. More of the gastric ulcers were completely cured (95.8 per cent) than of any other type, and all of them were either cured or improved. Of the duodenal ulcers 79.4 per cent were cured and 13.7 per cent im-

TABLE III

RESULTS FROM SUBTOTAL GASTRIC RESECTION IN 113 PATIENTS WITH PEPTIC ULCER PERFORMED FROM 1938 TO 1945

| Present Condition | Number of Cases by Location of Lesion | | | | | |
|---|---|---|---|---|---|---|
| | Gastric (Per Cent) | Duodenal (Per Cent) | Gastric and Duod. (Per Cent) | Marginal (Per Cent) | Total (Per Cent) | Total of Primary Resections (Per Cent) |
| Cured | 23 (95.8) | 58 (79.4) | 7 (70.) | 2 (33.3) | 90 (79.6) | 88 (82.3) |
| Improved | 1 (4.2) | 10 (13.7) | 0 (0) | 0 (0) | 11 (9.7) | 11 (10.3) |
| Unimproved | 0 (0) | 3 (4.1) | 3 (30.) | 3 (50.) | 9 (8.0) | 6 (5.6) |
| Died, postoperatively | 0 (0) | 1 (1.4) | 0 (0) | 0 (0) | 1 (0.9) | 1 (0.9) |
| Died, subsequently | 0 (0) | 1 (1.4) | 0 (0) | 1 (16.6) | 2 (1.8) | 1 (0.9) |
| Total number | 24 (100) | 73 (100) | 10 (100) | 6 (100) | 113 (100) | 107 (100) |

proved, a total of 93.1 per cent. When both a gastric and a duodenal ulcer were present the result was less favorable, 70 per cent cured, and for the ulcer that developed in the stomal area after a previous gastroenterostomy, it was largely unfavorable (only one-third cured). If the latter cases are excluded, the results for primary operation are found (last column) and they indicate complete cure in 82.3 per cent with improvement in an extra 10.3 per cent, a favorable result in 92.6 per cent.

In order to test the reliability of our data on the more recently operated cases, Table IV shows a break-down of the results in the total 110 surviving patients for the period of their follow-up. It will be noted that for the first, second and third years after resection the percentage of those cured and of those improved, taken together, is approximately the same (91.8, 90 and 89.6). For those operated four and for those five or more years previously the combined cured and improved percentage was only slightly less favorable (87.9 and 87.5). Thus it is obvious on the basis of our data, that an almost equally favorable result from gastric resection may be expected after five years, there occurring only a slight decrease with each succeeding year.

TABLE IV

RESULTS FROM GASTRIC RESECTION IN 110 SURVIVING PATIENTS WITH PEPTIC ULCER ACCORDING TO TIME AFTER OPERATION (1938–1945 INCLUSIVE)

| Time after Operation | Total Number | Physical Status | | |
|---|---|---|---|---|
| | | Cured | Improved | Unimproved |
| Under 1 year | 110 | 90 (81.8) | 11 (10.1) | 9 (8.2) |
| 2 years | 70 | 58 (82.9) | 5 (7.1) | 7 (10.0) |
| 3 years | 47 | 39 (81.3) | 4 (8.3) | 5 (10.4) |
| 4 years | 33 | 26 (78.8) | 3 (9.1) | 4 (12.1) |
| 5 or more years | 16 | 12 (75.) | 2 (12.5) | 2 (12.5) |

The unimproved patients, including those who died, are covered more specifically in Table v. This shows that of the three patients who died, one (F. W.) succumbed on

TABLE V

SPECIAL DATA ON TWELVE PATIENTS WHO WERE UNIMPROVED, INCLUDING THREE WHO DIED

| Initials | Sex/Age | Location of Ulcer | Reason for Operation | Amount of Stomach Removed | Ulcer and Pylorus Removed | Previous Surgery | Postoperative Acidity, Free/Total | Subsequent Developments | Possible Explanation for Unfavorable Results |
|---|---|---|---|---|---|---|---|---|---|
| F. W. | M/50 | D. | Hem. | ⅔ | Yes | None | ..... | Death on 4th p.o. day with peritonitis secondary to subphrenic abscess. | Diabetes. Preoperative perforation. |
| A. P. | M/62 | D. | Sten. Refr. | ⅓ | No | None | 0/32* | Duodenal stump perforated 13th day. Died of hem. 12th mo. *X*-ray negative. | Inadequate resection. Ulcer not removed. |
| J. S. | M/57 | M. | Hem. | ⅓ | Yes | 13 yrs.: gastroenterostomy. | 18/26 | Jejunal ulcer perforated at 6 mos. Then repeated hemorrhages. Died 27 months. | Inadequate resection with secondary operation. Continued acid secretion. |
| Q. M. | M/48 | D. | Hem. | ⅓ | No | None | ..... | Jejunal ulcer perforated after 4 months. | Inadequate resection. Ulcer and pylorus not removed. |
| N. S. | M/27 | D. | Refr. | ⅔ | No | 6 yrs.; perforation oversewn. | 0/14* | Vomiting, nervousness and weakness, but no pain for 6 yrs. *X*-ray negative for dumping. | Secondary operation; ulcer and pylorus not removed. Functional intestinal disturbance. Uncooperative. |
| A. D. | M/27 | D. | Refr. | ½ | No | None | 5/15* | Hemorrhaged 7th and 13th p.o. days. Recurrent symptoms after 3 years. | Allergic. Inadequate resection. Ulcer and pylorus not removed. |
| D. S. | M/33 | G, D. | Hem. Refr. | ⅓ | Yes | None | 30/50 | Jejunal ulcer in 6 mos. Additional resection in 22 mos., but ulceration and free acid persist. | Associated gastritis and alcoholic. Inadequate resection and continued acid secretion. |
| B. L. | F/61 | G, D. | Hem. | ½ | G-yes D-no | None | ..... | Recurrent hemorrhages after 1 year. *X*-ray negative for stomal ulcer. | Inadequate resection. Duodenal ulcer not removed. Psychoneurotic. |
| T. C. | M/26 | G, D. | Hem. Refr. | ⅗ | No | None | 30/40 | Jejunal ulcer after 2 years. | Alcoholic and uncooperative. Inadequate psychopath. Ulcer and pylorus not removed. Continued acid secretion. |
| A. K. | M/59 | M. | Hem. Refr. | ⅔ | Yes | 23 years; pylorectomy and gastro-enterostomy. | ..... | Repeated hemorrhages. | Associated hemorrhagic gastritis. Secondary operation. |

TABLE V.—(*Continued*)

| Initials | Sex/Age | Location of Ulcer | Reason for Operation | Amount of Stomach Removed | Ulcer and Pylorus Removed | Previous Surgery | Postoperative Acidity, Free/Total | Subsequent Developments | Possible Explanation for Unfavorable Results |
|---|---|---|---|---|---|---|---|---|---|
| W. R. | M/30 | M. | Refr. | ⅔ | Yes | 18 mos.; pylorectomy and gastroenterostomy, 4 mos.; excision of stomal ulcer. | 0/32* | 65 lbs. wt. loss, weakness and partial intermittent internal obstruction. | Secondary operation. Total of seven abdominal operations. |
| L. K. | M/59 | M. | Hem. | ⅔ | Yes | 7 years; gastroenterostomy. | 40/52 | Recurrent jejunal ulcer. | Secondary operation. Psychoneurotic. Continued acid secretion. |

* After histamine.

the fourth postoperative day and the death due to peritonitis secondary to a subdiaphragmatic abscess which had resulted from perforation prior to resection. The second death occurred in a patient (A. P.) whose duodenal stump perforated at the end of the second week and who required for that a second operation. He then recovered, but a year later died as a result of repeated hemorrhage. The final death occurred in a patient (J. S.) who had had a gastroenterostomy in 1924, was resected in 1938 and then developed a marginal ulcer that required further resection in 1939; he again developed an ulcer with recurrent hemorrhage and died in the twenty-seventh month after his original resection.

Analysis of the data in Table v for the total group of twelve cases, in which the results were unfavorable, reveals: (1) that six had one-half or less of the stomach removed, and, with some overlapping, that six of them did not have the ulcer itself removed (a total of eight in one or the other or both categories); (2) that of the remaining four cases, three (A. K., W. R. and L. K.), as well as two of the above eight, had had previous surgery on the stomach and the other patient (F. W.) had a subphrenic abscess at the time of the resection; and (3) that four of the total group were psychoneurotic (one a confirmed psychopath), that two of these were alcoholic and that a fifth patient was highly uncooperative in the subsequent management of his case.

Postoperative gastric analyses were not done routinely in the series but of the unimproved patients it will be noted that two had a free acidity of 30 units and one of 40 units (the latter one having had two thirds of the stomach removed).

The failure to regain weight after a gastric resection has been noted by various authors, and so in Table vi are presented certain data on this subject in 100 of our cases. More than half of them (52 per cent) were five or more pounds under their usual weight at the time of the last follow-up examination, and their average weight loss was 19.6 pounds. Only 13 per cent had gained more than five pounds, while 35 per cent remained at about the same weight. Weight loss was most frequently encountered in the duodenal and marginal ulcer cases (56.1 and 60 per cent, respectively).

TABLE VI

WEIGHT CHANGES GREATER THAN 5 POUNDS IN 100 PATIENTS WITH PEPTIC ULCER FOLLOWING GASTRIC RESECTION (1938–1945)

| Type of Ulcer | Gained | | Lost | | Unchanged | Total of Each type |
|---|---|---|---|---|---|---|
| | Number, Per Cent | Average gain in lbs. | Number, Per Cent | Average loss in lbs. | Number, Per Cent | |
| Gastric | 5 (23.8) | 10.8 | 9 (42.9) | 16.6 | 7 (33.3) | 21 (100.) |
| Duodenal | 4 (6) | 11.5 | 37 (56.1) | 18.5 | 25 (37.9) | 66 (100.) |
| Gastroduodenal | 3 (37.5) | 13.0 | 3 (37.5) | 24.3 | 2 (25.0) | 8 (100.) |
| Marginal | 1 (20.0) | 10.0 | 3 (60.0) | 38.0 | 1 (20.0) | 5 (100.) |
| Totals | 13 | | 52 | | 35 | 100 |
| Wt. change average, in lbs | | 11.5 | | 19.6 | | |

## COMMENTS

The data obtained in this series of peptic ulcer cases subjected to subtotal gastric resection are at variance with some of those reported in the surgical literature for the past six years. Mage,[1] in a report on 600 patients who survived the operation at the Mt. Sinai Hospital in New York City between 1923 and 1940, found recurrent ulceration in forty-one, ulcer symptoms without convincing evidence of such recurrence in ten, and some disturbance of gastric function, presumably due to the operation itself, in an additional sixty. Thus, excluding his operative mortality, he had unsatisfactory results in 18 per cent. Heuer,[2] in a careful analysis of his personal experience with 139 patients followed from one to ten years, had unsatisfactory results in 15.1 per cent; this, however, including his operative mortality of 7 per cent. In a review of the literature he found that nineteen authors, together covering 1,196 cases only 67 per cent of which were followed, had a similar result for a shorter period, one to five years, while twenty-two authors, for a one to twenty-year period, admitted failure in 17.3 per cent. In his own series of cases followed from five to ten years, only two-thirds were entirely relieved of symptoms. Walters, Lewis and Lemon,[3] reporting on 197 patients with duodenal ulcer operated upon and followed at the Mayo Clinic from 1929 to 1939, found that only 2.5 per cent developed a recurrent anastomotic ulcer, though an additional 14 per cent had subsequent gastric symptoms. Rienhof,[4] on the other hand, has reported 90 per cent eventually cured or improved in a series of 260 duodenal cases, though twenty-six of these patients required reoperation; Miller[5] reported 90 per cent cured and the remaining 10 per cent improved in a series of 173 patients who survived the operation (mortality, 2.8 per cent). Wangensteen[6] has reported a very remarkable result in 300 consecutive gastric, duodenal and gastrojejunal patients, having had no ulcer recurrence. He does not, however, give the number that had subsequent digestive symptoms. Kiefer,[7] of the Lahey Clinic, reported on 222 survivors of resection, having had no ulcer recurrence in forty-nine gastric cases, but apparently 9.6 per cent in 146 duodenal cases and 22.2 per cent in 27 marginal cases. Allen and

Welch,[8] also of Boston, had but two recurrences in forty-three survivors from resection for duodenal ulcer before 1938, and no recurrences in seventy-one survivors of 76 patients operated upon after that time.

The postoperative mortality has varied considerably. Heuer's[2] review of the literature showed an average mortality of 6.8 per cent, and his own was slightly higher. He admits, however, that the rate has been steadily declining. Lahey and Marshall[9] found theirs to be 2.7 per cent, exclusive of those with a gastrojejunocolic fistulous tract; 3.2, when the fistulous tracts were included, and 4.4 for gastrojejunal ulcer alone. Only 2 per cent of Rienhof's patients died postoperatively. These figures may be compared with ours of 0.9 per cent.

The literature reveals that the results have *not* been particularly favorable in the patients who had had previous gastric surgery (secondary resection). Holman and Chenowith,[10] in twenty-six such cases, got a good result in only nineteen (73 per cent). Sanders[11] had a mortality of 3.6 per cent in twenty-eight previously operated patients as against 2.7 for his seventy-three primary resections. In our series it has been shown that of the twelve unimproved patients, five had had previous gastric surgery, and that of the six resected for a marginal ulcer, only two are recorded as cured. This may be contrasted with cure or definite improvement in 92.6 per cent of our patients undergoing a primary resection.

Another unfavorable factor in the results from gastric resection would seem to be the failure on the part of the surgeon to remove the ulcer itself and an adequate portion of the stomach. Kiefer[7] reported seven recurrent ulcers and three postoperative hemorrhages in thirty patients in whom the pylorus and duodenum were not included in the resection. Even when the portion of the duodenum that includes the ulcerative lesion cannot be removed Allen and Welch[8] have insisted that the mucosa of the antrum and duodenal cap should be excised. Furthermore, it is now the generally accepted opinion among surgeons that in all instances, one-half to two-thirds of the stomach should be excised. Wangensteen insists on a removal of three-fourths of the stomach and always of the antral mucosa. In six of our twelve patients who did badly after operation the ulcer had not been removed, and in four of these six, and in two others, one-half or less of the stomach had been resected.

The final unfavorable factor, and one that especially interests the gastroenterologist, has to do with the emotional state of the patient, his personal habits and his ability and willingness to cooperate. As already stated, four of our unimproved patients were clearly psychoneurotic, two of them also being alcoholic, and one other patient failed entirely to cooperate in his subsequent management.

These observations consequently suggest that the poor results from subtotal gastric resection may be blamed, in part, on an inadequate operative procedure and, in part, on an inadequate personality of the patient. This is not intended to imply that the surgeon should in every case remove the ulcer-bearing area and more than half of the stomach or that the internist should refuse to sanction surgical interference in the psychoneurotic patient. In many instances, as we believe was true for most of our series of unimproved patients, the ideal operative procedure may be technically inadvisable and no other form of therapy may be regarded as justifiable. At the same time these observations indicate the conditions under which a somewhat guarded prognosis must be entertained. Furthermore, when such conditions can be eliminated in the individual patient, one is enabled to present a more hopeful outlook.

Ingelfinger,[12] in a review of the physio-

logical disturbances of the patient who has had a gastrectomy, emphasizes the frequency of reduced weight and calls attention to the confirmatory observations of Church and Hinton,[13] of Browne and McHardy,[14] and of Miller.[5] He details, however, certain evidence to indicate that eventually the tendency to remain underweight is less marked. In an attempt to explain the early weight loss, Ingelfinger discusses the "dumping syndrome," due to overfilling of the jejunum from quick emptying of the stomach, with a consequent feeling of fullness, nausea, weakness and giddiness. In spite of his estimate of a 10 per cent incidence of postgastrectomy indigestion, however, only two of our patients have had, even transiently, phenomena suggestive of the "dumping syndrome" or any other digestive disturbance. In fact, in most instances the appetite has been good and the intake of food equal to or in excess of that previously consumed. Ingelfinger also refers to defects in absorption from the intestine after gastrectomy, and more recently, Wollaeger, Comfort, Weir and Osterberg,[15] of the Mayo Clinic, have demonstrated conclusively a deficiency of fat absorption after gastric resection, which is the most probable explanation for the difficulty in gaining weight. In a series of carefully studied subjects they found the amount and percentage of total lipids in the stools of the gastrectomized cases to average more than twice that of controls, the increase being most marked in those with postcibal distress. Among the possible factors for this loss of fats and calories in the feces, they mention rapid emptying of the stomach, intestinal hurry and a diminished flow of pancreatic and biliary secretions.

The significance of allergy in relation to the after-effects of subtotal gastrectomy is uncertain. One of our patients who was allergic to certain food substances did poorly, bled on the seventh and thirteenth postoperative days and after three years had a recurrence of symptoms, but he also had an inadequate resection and the duodenal ulcer was not removed. Another highly allergic patient since his resection has had no difficulty in eating all of the foods that previously caused severe gastrointestinal upsets. In this patient, as in many others, there has been no impairment of appetite, his intake of food has been much greater than before operation, his physical and mental activities have not been impaired, and yet his weight is persistently about 20 pounds below his previous average.

## CONCLUSIONS

An analysis of the results in 113 cases of peptic ulcer subjected to partial gastric resection over an eight-year period leads to the following conclusions:

1. The unfavorable factors in the clinical results are: (1) Lack of cooperation on the part of the patient, (2) failure on the part of the surgeon to remove the ulcer, or at least the pyloric mucosa, and one-half or more of the stomach, and (3) previous gastric surgery.

2. When these factors are eliminated and the surgical technic is good, a favorable result may be anticipated in 95 per cent or more of the cases.

3. In the series of cases herein presented primary resection led to cure or marked improvement in 100 per cent of the patients with gastric ulcer and in 92.6 per cent of the patients with duodenal ulcer.

## REFERENCES

1. Mage, S. Recurrent ulceration following subtotal gastrectomy in treatment of gastroduodenal ulcer. *Ann. Surg.*, 116: 729, 1942.
2. Heuer, G. J. The Treatment of Peptic Ulcer. Philadelphia, 1944. J. B. Lippincott Company.
3. Walters, W., Lewis, E. B. and Lemon, R. G. Primary partial gastrectomy (Polya type) for duodenal ulcer: study of results in 212 cases. *Surg., Gynec. & Obst.*, 71: 240, 1940.
4. Rienhof, W. F., Jr. Analysis of results of surgical treatment of 260 consecutive cases of chronic

peptic ulcer of the duodenum. *Ann. Surg.*, 121: 583, 1945.

5. Miller, G. G. Report on 230 cases of subtotal gastric resection for peptic ulcer. *Surgery*, 12: 383, 1942.
6. Wangensteen, O. H. Causes of failure after gastric resection for ulcer. *Wisconsin M. J.*, 44: 878, 1945.
7. Kiefer, E. O. Jejunal ulcers and recurrent hemorrhages after partial and subtotal gastrectomy for peptic ulcer. *J. A. M. A.*, 120: 819, 1942.
8. Allen, A. W. and Welch, C. E. Gastric resection for duodenal ulcer: follow-up studies. *Ann. Surg.*, 115: 530, 1942.
9. Lahey, F. H. and Marshall, S. F. Surgical management of some of the more complicated problems of peptic ulcer. *Surg., Gynec. & Obst.*, 76: 641, 1943.
10. Holman, C. and Chenoweth, A. Problems of treatment of secondary peptic ulcer. *Surg., Gynec. & Obst.*, 75: 314, 1942.
11. Sanders, R. L. Review of 101 subtotal gastrectomies for benign ulcer. *Surgery*, 18: 229, 1945.
12. Ingelfinger, F. J. Medical progress; late effects of total and subtotal gastrectomy. *New England J. Med.*, 231: 321, 1944.
13. Church, R. E. and Hinton, J. W. Follow-up results in subtotal gastric resection for ulcer. *Am. J. Digest. Dis.*, 9: 317, 1942.
14. Browne, D. C. and McHardy, G. Patient after gastric surgery. *South. M. J.*, 36: 32, 1943.
15. Wollaeger, E. F., Comfort, M. W., Weir, J. F. and Osterberg, A. E. Total solids, fat and nitrogen in the feces; II. a study of persons who had undergone partial gastrectomy with anastomosis of the entire cut end of the stomach and the jejunum (polya anastomosis). *Gastroenterology*, 6: 93, 1946.

# The Nisulfazole Treatment of Chronic Ulcerative Colitis*

RALPH H. MAJOR, M.D.
KANSAS CITY, KANSAS

FOLLOWING the discovery that sulfanilamide had marked therapeutic value, many investigators became interested in the possible value of various derivatives. We became interested in the investigation of nitrobenzene compounds and studied first the analogue of sulfanilamide, *p*-nitrobenzosulfonamide. This compound, when tested with streptococci and pneumococci, showed a high bactericidal value but had such toxicity that its clinical employment was not undertaken. With the appearance of sulfapyridine and sulfathiazole, the nitro analogues, 2-(*p*-nitrobenzenesulfonamido)-pyridine and 2-(*p*-nitrobenzenesulfamido)-thiazole, were produced and their properties studied. The studies showed that these two compounds were not readily absorbed from the intestines, an observation which suggested their use in intestinal infections. As the compound 2-(*p*-nitrobenzene-sulfonamido)-pyridine was less readily absorbed, its effects on a patient suffering with ulcerative colitis were studied, with results so encouraging that we began a systematic study of its effects in chronic idiopathic ulcerative colitis. For purposes of simplification, 2-(*p*-nitrobenzenesulfonamido)-pyridine was called Nisulfadine, and 2-(*p*-nitrobenzenesulfonamido)-thiazole was called Nisulfazole. (Fig. 1.)

Our first report was in 1942[1] and included five cases; all the patients were treated with both compounds and showed encouraging results. A second report[2] in 1944 included fifteen patients and a third report,[3] which included patients seen up to 1946, describes twenty-one cases. The present paper includes thirty-seven patients who have been followed the past five years.

We realize the criteria for the diagnosis of chronic ulcerative colitis are not as clear as we might desire. The causative factor or the causative organism is uncertain, so there cannot be the convincing demonstration of an etiological agent such as the Entamoeba histolytica in amebic dysentery, or the Bacillus dysenteriae in acute or chronic dysentery. The absence of these organisms in all cases, however, removes two large groups of chronic dysenteries from consideration.

All of the cases treated were diagnosed chronic ulcerative colitis after proctoscopic examination showed the presence of ulcers and the *x*-ray showed the characteristic picture of "feathering" of the walls of the intestine, loss of haustration and the presence of the characteristic "garden hose" type of colon.

Anemia of the secondary type was a very common finding in our patients before treatment. Eighteen of the thirty-seven patients showed a red cell count below 4,000,000, twenty-six showed a hemoglobin below 80 per cent (12.4 Gm.). Five patients showed a red cell count below 3,000,000, eleven patients showed a hemoglobin below 60 per cent (9.5 Gm.). The lowest red cell count was 2,650,000, the lowest hemoglobin 35 per cent (5.5 Gm.). The severe anemia

* From the Department of Internal Medicine, University of Kansas School of Medicine, Kansas City, Kansas.

so frequently seen in our patients apparently was not caused by the loss of blood since some of the patients having the most severe anemia passed only insignificant amounts of blood. There seems to be a definite tendency in this disease to develop anemia. Many patients followed after dismissal from the hospital showed a persistent tendency to develop anemia although the diarrhea had been checked and the stools had become normal.

In contrast to the anemic group, the patients with red cell count above 4,000,000 outnumbered those below, although only eleven of the thirty-seven patients showed a hemoglobin above 80 per cent. The patients without a severe secondary anemia usually made a more rapid and more lasting recovery. The patients who had the most severe diarrhea usually showed the greatest degree of anemia although one patient who, on admission, had fifteen stools in twenty-four hours showed a red blood count of 4,730,000, hemoglobin 87 per cent (13.5 Gm.), and another patient who had twelve stools daily showed a red blood count of 4,500,000, hemoglobin 81 per cent (12.5 Gm.).

Chopra and Chakravarty[4] found gastric hypochlorhydria very frequent in chronic ulcerative colitis. This point was investigated in twenty of our patients, employing the alcohol test meal which was also used by Chopra and Chakravarty. We employed the four-test fractional meal and found that, according to Napier's classification, only two patients showed hyperacidity above 65 in any specimen. The other patients showed either a low normal, 10 to 25, or achlorhydria. Our interpretation of the results of the gastric analyses is that the gastric acidity is quite variable or even absent in chronic ulcerative colitis.

Our studies in this series of patients have added nothing to our concepts of the etiology of this disease. The stool cultures showed only the normal bacterial inhabitants of the intestinal tract. Many of the patients showed some degree of emotional instability but the percentage was not higher than that seen in a routine check of hospital patients. In some patients, emotional upsets undoubtedly aggravated the patient's condition, but we have had the same experience repeatedly in patients with cardiac disease, with arterial hypertension and with lobar pneumonia. The mental state aggravates the patient's condition in a variety of diseases. There is certainly a mental factor in ulcerative colitis; and while we cannot agree with the inclusive title of Daniels's paper, "Nonspecific Ulcerative Colitis as a Psychosomatic Disease,"[5] we readily agree with his conclusion that "A carefully taken psychosomatic history should be included in all cases of ulcerative colitis."

Because of the suggestion that chronic ulcerative colitis might possibly be a form of lymphogranuloma venereum, Frei tests were performed on all patients. Only one showed a faintly positive reaction, which is additional confirmation of the statement of Rodaniche, Kirsner and Palmer[6] that the virus of lymphogranuloma venereum is "in no way involved in the great majority of cases."

The ages of our patients varied between six years and seventy-one years. Grouped into decades, the first decade comprised thirteen cases, the second decade seven cases, the third eight, the fourth three, the fifth four, the sixth and seventh two cases.

The duration of the disease showed great variation, from one month to eighteen years. Seven cases had a duration of less than six months; twenty-five cases had a duration greater than one year. The most prompt response to treatment, as one might anticipate, appeared in the patients showing the lowest chronicity; these patients also showed the most permanent results.

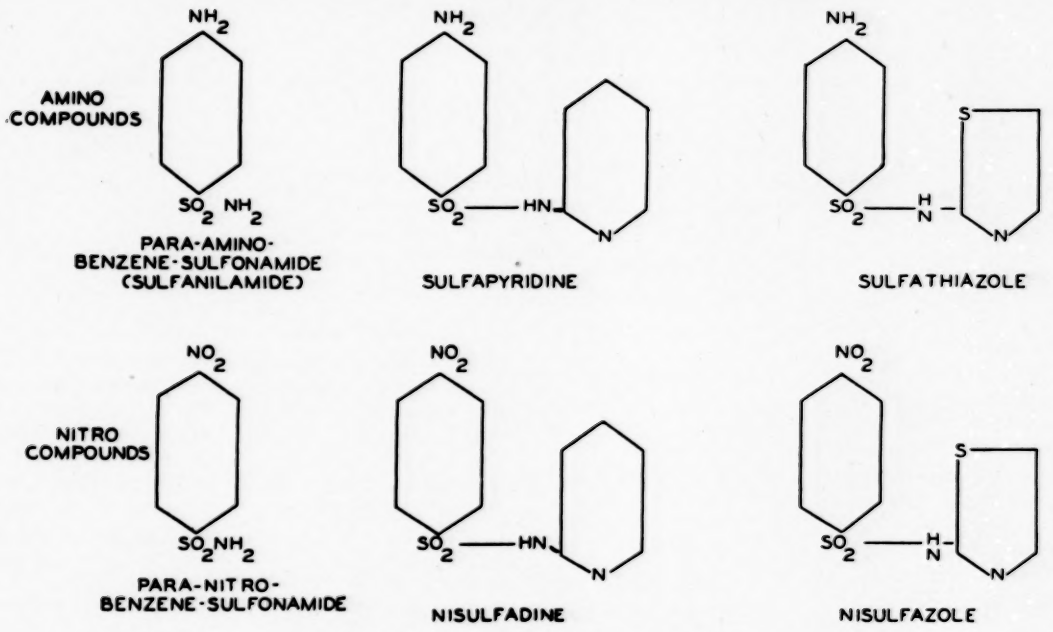



FIG. 1. Amino and nitro compounds.

The general treatment of the patients followed the lines usually recommended in the treatment of this disease. The patients were placed on a bland, residue-free diet and encouraged to partake freely of fluids. If the patient had lost much fluid from watery evacuations, subcutaneous normal saline infusions were administered. If the patient had very frequent stools, laudanum or paregoric was administered; and if they suffered from tenesmus, belladonna or trasentin was employed. Patients showing marked anemia were given blood transfusions.

Nisulfazole was administered in the early cases only by mouth, either in tablets, capsules or enteric coated tablets. The enteric coated tablets were employed in patients who developed nausea, but often proved unsatisfactory as patients who had a very active diarrhea often passed these tablets undissolved. The initial dose by mouth varies from 4 to 6 Gm. in twenty-four hours. If nausea developed, the drug was withdrawn for twenty-four hours and then medication was resumed with a dosage of 2 or 3 Gm. daily.

Nisulfazole, when administered by mouth, is partially transformed into sulfathiazole and both compounds appear in the blood. Table I shows a typical example.

TABLE I
NISULFAZOLE AND SULFATHIAZOLE BLOOD LEVELS
R. T., age 19, No. 4 of Table II

| | Mg. per 100 cc. of Blood | | Dosage of Nisulfazole |
|---|---|---|---|
| | Nisulfazole | Sulfathiazole | |
| 2/27/42 | 8.8 | 1.4 | 4 Gm. daily in 4 equal doses |
| 3/3/42 | 9.1 | 1.5 | |
| 3/6/42 | 9.6 | 1.4 | |
| 3/11/42 | 9.2 | 1.15 | |
| 3/13/42 | 9.8 | 1.7 | |
| 3/18/42 | 8.6 | 1.5 | |
| 3/21/42 | 6.6 | 0.7 | |
| 3/24/42 | 10.5 | 2.5 | 6 Gm. daily in 4 equal doses |
| 3/27/42 | 11.8 | 1.4 | Drug discontinued because of nausea |

The degree of absorption as measured by the blood values varied in different patients. Thus one patient, No. 5, on a daily dosage of 3 Gm. of nisulfazole, showed blood

TABLE II

SUMMARY OF RESULTS

| | Age | Sex | Duration | Admitted | No. Stools Daily on | | Length of Treatment in Hosp. | Result on Dismissal | Relapse | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Admission | Dismissal | | | | |
| 1 | 71 | M | 18 mo. | 6/23/41 | 10 | 2 | 1 mo. | Recovery | None | Died "heart attack" (coronary occlusion?) 10/19/43 |
| 2 | 16 | M | 4 mo. | 6/30/41 | 18 | 2 | 3 wk. | Recovery | One slight | Died pneumonia 1/18/44 |
| 3 | 23 | M | 14 mo. | 7/28/41 | 14 | 2 | 5 mo. | Recovery | Two slight | Markedly improved 6/20/46. Rarely has symptoms. No medication for 2½ yrs. |
| 4 | 19 | F | 9 mo. | 1/19/42 | 10 | 2 | 4 wk. | Recovery | One slight | "Well" 11/23/45. No medication for 2 yrs. Has gained 20 lbs. Normal *x*-ray 7/1/42 |
| 5 | 22 | F | 5 mo. | 2/13/42 | 27 | 3 | 2 mo. | Recovery | None | Died later, cause unknown; no diarrhea |
| 6 | 19 | M | 30 mo. | 7/23/42 | 8 | 3 | 3 mo. | Improved | Two | Died at home 12/21/44 (pneumonia?) |
| 7 | 37 | F | 12 mo. | 8/4/42 | 20 | 2 | 10 wk. | Recovery | None | "Well" 6/20/46. No medication for 1 yr. Has gained 53 lbs. Normal *x*-ray 5/15/45 |
| 8 | 18 | F | 6 yr. | 1/16/43 | 7 | 1 | 1 mo. | Recovery | None | "Well" 1/14/44. No medication for 2 yrs. |
| 9 | 54 | M | 3 yr. | 1/19/43 | 18 | 2 | 4 mo. | Improved | None | Improved 6/20/46. No medication for 2 yrs. Colostomy 3/8/43 |
| 10 | 40 | M | 5 mo. | 8/2/43 | 8 | 2 | 1 mo. | Recovery | None | "Perfectly well" 6/20/46. No medication for 1 yr. Normal *x*-ray 6/24/44 |
| 11 | 41 | F | 1 mo. | 10/24/43 | 10 | 1 | 10 wk. | Recovery | None | "Well, feeling fine" 5/18/45. No medication for 1 yr. |
| 12 | 37 | F | 4 mo. | 3/14/44 | 6 | 1 | 3 mo. | Recovery | None | "Well" 6/20/46. No medication for 1 yr. Has gained 30 lbs. Normal *x*-ray 5/24/44 |
| 13 | 13 | M | 5 yr. | 8/22/44 | 12 | 2 | 1 mo. | Recovery | One slight | Symptom-free 6/20/46. No medication past six months |
| 14 | 30 | F | 3 yr. | 10/22/44 | 15 | 2 | 2 mo. | Recovery | None | "Well" 10/2/45. No medication for 1 yr. Nearly normal *x*-ray 12/21/44 |
| 15 | 18 | F | 7 mo. | 10/31/44 | 18 | 1 | 2 mo. | Recovery | Two slight | Symptom-free 5/18/46 |
| 16 | 27 | F | 4 yr. | 11/25/44 | 20 | 2 | 4 mo. | Recovery | None | Symptom-free 6/20/46. Complicated by intestinal polyposis. Colectomy planned |
| 17 | 14 | M | 10 yr. | 1/24/45 | 8 | 2 | 3 wk. | Recovery | None | "Well" 6/20/46. No medication for 1 yr. |
| 18 | 55 | M | 18 yr. | 3/1/45 | 8 | 2 | 6 wk. | Recovery | One slight | Improved 7/10/46. Nisulfazole medication continues |
| 19 | 24 | F | 12 yr. | 3/10/45 | 7 | 2 | 1 mo. | Recovery | None | Symptom-free 7/10/46. Nisulfazole medication. Permanent stricture |
| 20 | 44 | M | 11 yr. | 4/14/45 | 4 | 1 | 2 wk. | Recovery | None | Symptom-free 7/25/46. Nisulfazole medication |
| 21 | 6 | M | 1 yr. | 5/25/44 | 4 | 1 | 6 wk. | Recovery | One | Symptom-free 6/3/46. Nisulfazole medication |
| 22 | 53 | M | 2 mo. | 7/14/45 | 8 | 1 | 1 mo. | Recovery | None | "Well" 6/20/46. No medication for 6 mo. |
| 23 | 13 | M | 2 yr. | 8/2/45 | 5 | 1 | 2 wk. | Recovery | None | Well |

TABLE II (*Continued*)

| | Age | Sex | Duration | Admitted | No. Stools Daily on | | Length of Treatment in Hosp. | Result on Dismissal | Relapse | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Admission | Dismissal | | | | |
| 24 | 13 | M | 6 yr. | 10/27/45 | 6 | 1 | 6 wk. | Recovery | None | Symptom-free 6/20/46. No medication for 3 mo. Stricture of descending colon |
| 25 | 53 | M | 3 yr. | 11/14/45 | 3 | 1 | 2 wk. | Recovery | None | Symptom-free 6/20/46. Nisulfazole medication |
| 26 | 24 | M | 3 mo. | 11/28/45 | 5 | 1 | 1 mo. | Recovery | None | Symptom-free 6/20/46. Nisulfazole medication |
| 27 | 32 | F | 7 mo. | 12/17/45 | 20 | 1 | 5 wk. | Recovery | None | Symptom-free 6/20/46. Nisulfazole medication |
| 28 | 28 | M | 11 yr. | 12/31/45 | 15 | 1 | 6 wk. | Recovery | None | Symptom-free 6/15/46. Nisulfazole medication. |
| 29 | 33 | M | 2 yr. | 12/31/45 | 5 | 1 | 1 wk. | Recovery | None | Symptom-free 7/10/46. Nisulfazole medication |
| 30 | 14 | M | 9 yr. | 1/18/46 | 10 | 1 | 3 mo. | Recovery | One | Symptom-free 6/6/46. Nisulfazole medication |
| 31 | 69 | F | 2½ yr. | 2/27/46 | 4 | 1 | 6 wk. | Recovrey | None | Symptom-free 6/10/46. Nisulfazole medication |
| 32 | 35 | M | 5 yr. | 4/23/46 | 3 | 1 | 3 wk. | Recovery | None | Symptom-free 7/10/46. Nisulfazole medication |
| 33 | 19 | M | 6 yr. | 4/27/46 | 4 | 1 | 1 mo. | Recovery | None | Symptom-free 7/13/46. Nisulfazole medication |
| 34 | 32 | F | 6 yr. | 6/2/46 | 8 | 1 | 2 wk. | Recovery | None | Symptom-free 7/25/46. Nisulfazole medication |
| 35 | 32 | M | 6 yr. | 4/18/46 | 8 | 2 | 1 mo. | Recovery | One | Symptom-free 7/13/46. Nisulfazole medication. Two normal stools daily |
| 36 | 27 | M | 8 yr. | 6/30/46 | 12 | 3 | 2 wk. | Improved | None | Improved 7/18/46. Nisulfazole medication |
| 37 | 7 | M | 3 yr. | 11/26/45 | 10 | 1 | 1 mo. | Improved | One | Improved 7/15/46. Nisulfazole medication |

values for nisulfazole of 8.3 and 7.6 mg. per 100 cc. and for sulfathiazole of 0.9 mg. and 0.7 mg.; while another patient, No. 31, on the same dosage showed values for nisulfazole of 1.82 mg. and 0.88 mg. with no sulfathiazole present.

The relationship between the blood levels for nisulfazole and the appearance of nausea showed much variation. Some patients with a nisulfazole blood level of 9 mg. per 100 cc. showed no nausea while other patients developed nausea with a blood level of 5 mg. per 100 cc.

Later the drug was administered by rectum in pectin suspension, two or three instillations of 10 cc. of a 10 per cent suspension. This method of administration was equally effective and had the advantage of producing no nausea. While patients receiving nisulfazole only by mouth showed nisulfazole blood levels varying from 1.5 to 16.3 mg. per 100 cc., patients who received the drug by rectum in the same dosage rarely showed more than a faint trace of nisulfazole in the blood.

In looking over the summary of results obtained during the hospitalization of these patients (Table II), thirty-four of the thirty-seven cases are described as "recovered" while three are markedly improved. By "recovery" we mean that the patients were symptom-free and not passing more than two or three normal appearing, well formed stools daily. That these patients were not all

"well" is obvious from the fact that on dismissal the *x*-ray picture of the intestine still showed lack or diminution of the normal haustration and that ten of them subsequently suffered from relapses of varying degrees.

The causes of these relapses were not always clear. The most common cause assigned by the patients was dietary indiscretions. In two instances, however, relapse was accompanied by purulent maxillary sinusitis, in one patient by acute mononucleosis, in one patient by acute pyelitis and in one patient by erythema nodosum.

Under the caption "remarks," we have summarized the latest reports we have received from the patients. Where the term "well" is employed, it signifies the patient's own description. "Symptom-free" is employed to mean that the patient does not pass more than two stools daily, that the stools are normal in appearance and that no blood is evident.

It is also apparent that some of the patients described as "symptom-free" are still taking nisulfazole and some have taken it for a considerable period. No. 19 has taken nisulfazole in doses of 2 Gm. daily for seventeen months, while No. 21 has taken it in the same dosage for twenty-six months, and several other patients have taken it for several months after leaving the hospital. We have not seen any untoward effects following such long administration but have insisted that such patients remain under continued observation so that frequent blood counts and urinalyses can be carried out.

The mechanism of action of nisulfazole is not understood any better than the etiology of ulcerative colitis. Presumably the action is bacteriostatic. It has been suggested that the action of nisulfazole is due entirely to the fact that it is broken down in the intestinal tract into sulfathiazole and that its therapeutic effects are due to sulfathiazole. We believe this to be incorrect for we have been unable to obtain the same results with sulfathiazole or, for that matter, with any para-amidobenzosulfonamide compounds. During the war we were frequently unable to obtain nisulfazole and were forced to substitute in its place sulfathiazole, sulfapyridine, sulfadiazine and sulfamerazine. None of these compounds produced the same results, a difference promptly noticed by the patients themselves. It should also be noted that the patients we have treated with nisulfazole had almost without exception previously been treated with all the usual sulfonamide compounds and several had received penicillin and streptomycin without any favorable results.

We wish to point out that a survey of Table II shows that all the patients without exception have improved with nisulfazole therapy.

We wish again to repeat the concluding sentences of our paper published in 1944: "In a disease such as chronic ulcerative colitis, a disease noteworthy for its chronicity and its tendency to recurrence, it would be hazardous to assert that most of these patients are permanently cured. We do feel, however, that therapy with nisulfazole has given us better results than any other treatment with which we are familiar."

## REFERENCES

1. Major, Ralph H. and Douglas, Harry L. The treatment of ulcerative colitis with nisulfadine and nisulfazole. *J. Kansas M. Soc.*, 43: 287, 1942.
2. Major, Ralph H. The treatment of ulcerative colitis with nisulfadine and nisulfazole. *Tr. A. Am. Physicians*, 58:1 75, 1944.
3. Major, Ralph H. The treatment of ulcerative colitis with nisulfadine and nisulfazole. *J. Lab. & Clin. Med.*, 31: 219, 1946.
4. Chopra, Sir R. N. and Chakravarty, B. Gastric acidity in chronic ulcerative colitis. *Indian M. Gaz.*, 77: 68, 1942.
5. Daniels, George E. Nonspecific ulcerative colitis as a psychosomatic disease. *M. Clin. North America*, p. 593, 1944.
6. Rodaniche, E. C., Kirsner, J. B. and Palmer, W. L. Lymphogranuloma venereum in relation to chronic ulcerative colitis. *J. A. M. A.*, 115: 515, 1940.

# Rôle of Hyaluronidase in Human Infertility*

RAPHAEL KURZROK, M.D., SAMUEL L. LEONARD, PH.D. *and* HELEN CONRAD, B.S.
NEW YORK, NEW YORK

PROGRESS in the study of human infertility is a slow process. Occasionally, the impetus to a better understanding of the problem and to new therapeutic applications comes from observations which would seem to be entirely unrelated.

The cementing material of connective tissues is composed of substances known as mucopolysaccharides. Two such substances forming the extracellular ground substance of connective tissue are hyaluronate and chondroitin sulfate. The mucopolysaccharides are also found in the secretions of mucous membranes and glands. Karl Meyer in a recent review (1945) defines mucopolysaccharides as polysaccharides* which contain hexosamine as one component, occurring either in free form or obtained by chemical degradation from substances of higher molecular weight. The mucopolysaccharide with which we are here concerned is hyaluronic acid (or its salt, a hyaluronate). Hyaluronic acid was isolated by Meyer and Palmer (1936) from vitreous humor and umbilical cords. It is the simplest of the acid mucopolysaccharides, being made up of equimolar parts of acetyl glucosamine and glucuronic acid. It can be extracted from tissues with water and forms extremely viscous solutions if it has been prepared without the use of alkali or precipitation by glacial acetic acid. Hyaluronic acid has also been isolated from tumors and from group A hemolytic streptococci (Seastone, 1943). Meyer (1938) found that hyaluronic acid is co-precipitated with proteins in dilute acid. This reaction forms the basis for a test to be described below.

Hoffman and Duran-Reynals (1930) and McClean (1930) noted the existence in mammalian testes of factors which profoundly modify the permeability of connective tissue by their action on hyaluronic acid and later work established the wide distribution in nature of similar factors, which they found to be enzymic in character. Such factors were observed in bacteria by Duran-Reynals (1933) and by McClean (1936); in malignant tissue by Duran-Reynals and Stewart (1931) and by Boyand and McClean (1935); in snake venom by Duran-Reynals (1939); and in leeches by Claude (1937). Mann and Lutwak-Mann pointed out in a recent review (1944) that these observations give insight into the mechanism of the invasive power of certain virulent bacteria; they explain the reasons for the rapid spread in the body of poisonous snake venoms; they clarify the phenomenon of reduction of viscosity in such biological fluids as the synovial fluid; and afford a new approach to better understanding of the circumstances accompanying fertilization of the mammalian egg, as well as insight into certain factors involved in the problems of human infertility.

The factors which profoundly modify the permeability of connective tissue became known as "skin spreading factors," a term which originated from experiments designed to measure *in vivo* the increase in the

* Polysaccharides are a group of carbohydrates which contain more than three molecules of simple carbohydrates combined with each other.

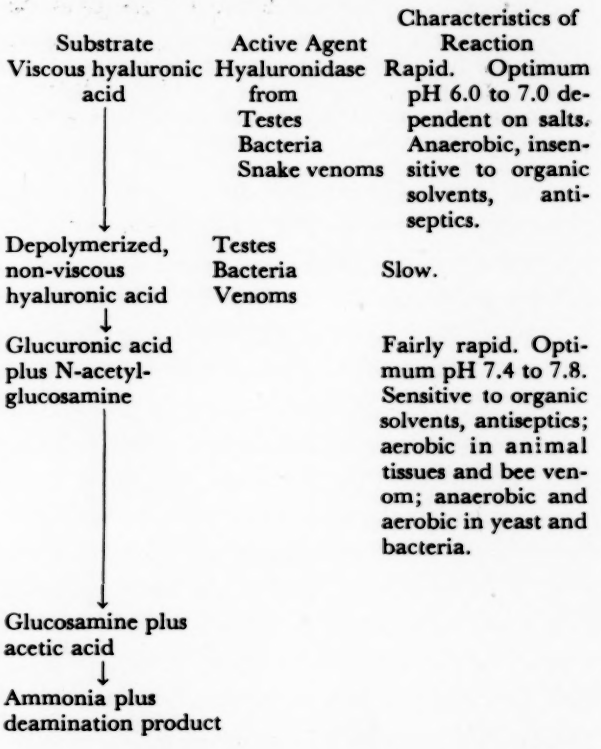
* From the Department of Obstetrics and Gynecology, Morrisania City Hospital, New York City, and the Department of Zoology, Cornell University, Ithaca, New York.

permeability of the dermis. Intracutaneous injection of such factors, together with a suitable indicator, causes the spreading or diffusion of the indicator over a wide area. The most accurate method appears to be that of Bacharach, Chance and Middleton (1940) which is based upon the measurement in rabbit skin of the total area through which a preparation of diffusing (spreading) factor spreads in a given time, compared with the area of spread of a standard preparation. Humphrey (1943) recently described a method which is based on the determination of the least amount of spreading factor required to produce a 20 per cent increase in the bleb area in guinea pig skin.

The substance effecting hydrolysis of the mucopolysaccharide hyaluronic acid has been termed "hyaluronidase" by Meyer and Palmer (1934, 1936). Chain and Duthie (1939, 1940) were the first to show that fairly pure preparations of testicular spreading factor also possess hyaluronidase activity. From the evidence so far available, it seems reasonable to conclude that the factor (enzyme or enzymes) responsible for diffusion in the dermis is identical with that exhibiting hyaluronidase activity, as measured by the viscosimetric and clot prevention tests (McClean, 1943; Lythgoe and Madinaveitia, 1943).

There are two methods available for the determination of the action of the enzyme hyaluronidase on hyaluronic acid: (1) *The Viscosimetric Assay:* The action of the enzyme produces a quantitative decrease in viscosity due to the depolymerization* of hyaluronic acid. (2) *The "Mucin Clot Prevention Test":* This is based on the fact that the addition of hyaluronic acid to acidified blood serum produces a mucin clot, an observation previously made by Karl Meyer (1938). When hyaluronidase depolymerizes hyaluronic acid, a clot will *not* form upon the addition of acidified serum. A recent description of the mucin clot prevention test is given by McClean (1943). It appears that the destruction of the clotting power of hyaluronic acid is an early stage in its degradation, which can be detected before any appreciable decrease in viscosity occurs.

Mann and Lutwak-Mann (1944) present the following scheme which illustrates the successive stages in the degradation of hyaluronic acid and its breakdown products.


Substrate
Active Agent
Characteristics of Reaction
Viscous hyaluronic acid
Hyaluronidase from
Testes
Bacteria
Snake venoms
Rapid. Optimum pH 6.0 to 7.0 dependent on salts. Anaerobic, insensitive to organic solvents, antiseptics.
Depolymerized, non-viscous hyaluronic acid
Testes
Bacteria
Venoms
Slow.
Glucuronic acid plus N-acetyl-glucosamine
Fairly rapid. Optimum pH 7.4 to 7.8. Sensitive to organic solvents, antiseptics; aerobic in animal tissues and bee venom; anaerobic and aerobic in yeast and bacteria.
Glucosamine plus acetic acid
Ammonia plus deamination product

The mammalian testis possesses in addition to hyaluronidase an enzyme system which deaminates and oxidizes amino sugars. The full implication of this is not yet understood.

The hyaluronidase activity of human semen was measured by Joël and Eichenberger (1945) and by Werthessen et al. (1945) by means of the viscosimetric test. Because of the inherent difficulties of this method, we prefer to assay hyaluronidase in semen by the mucin clot prevention test.

* The larger the molecule the greater is the viscosity of its solution. Hyaluronidase breaks up the long molecule of hyaluronic acid and thereby renders it less viscous.

Specific antisera can be produced in an animal by repeated injections of hyaluronidase preparations. By the addition of appropriate antisera, all activities of the enzyme can be neutralized, that is, the clot prevention, the fall in viscosity and the spreading effect in skin. These reactions are highly specific. McClean (1943) has shown that sera against bacterial hyaluronidase are species but not type-specific, and serum against diffusing factor from bull testis inhibits this enzyme but is ineffective against one made from mouse testis or derived from bacteria. Another interesting fact is the "adaptive" capacity of certain bacteria to react to the inclusion of hyaluronic acid in the medium by the production of increased amounts of hyaluronidase. McClean (1942) found that there is an inhibitor of the enzyme in the blood of the living animal, apparently linked to the pseudoglobulin fraction. Chondroitin sulfuric acid, heparin and depolymerized hyaluronic acid inhibit hyaluronidase, but glucuronate and glucosamine do not. The inhibition due to these substances is probably of the competitive type as the inhibitors are structurally similar to hyaluronic acid (Mann and Lutwak-Mann 1944). Leonard and Kurzrok (1946) have shown that blood from various species inhibits hyaluronidase when tested by the dispersion of follicle cells surrounding recently ovulated rat ova.

The problem of immediate concern is the part played by hyaluronidase in fertilization. McClean and Rowlands (1942) made the very interesting observation that hyaluronidase is capable of dispersing the follicle cells which surround recently ovulated mammalian ova. The follicle cells that surround the mammalian ovum are embedded in a transparent viscous gel which must be removed before the sperm can penetrate the egg. Hyaluronidase prepared from various sources (testes, bacteria, snake venom) was allowed to act on the recently ovulated ova. The follicle cells were dispersed without dissolution until the egg was left completely denuded. The enzyme action was found to be restricted apparently to the liquefaction of the gel (which probably contains hyaluronic acid) without affecting the ovum itself.* The authors point out that these observations could account for certain types of sterility as being due either to an insufficient concentration of hyaluronidase, as in instances of low sperm count, or else to an actual deficiency in the formation of the enzyme by the male organism. Fekete and Duran-Reynals (1943) confirmed the dispersing effect of hyaluronidase on the follicle cells surrounding the mouse ovum. Leonard and Kurzrok (1945) corroborated the observations on rat ova.

Rowlands (1944) reported a most significant observation. In a series of experiments on rabbits he determined the approximate number of sperm necessary for fertilization. For maximum fertility one million or more sperm are required, while 100,000 sperm are incapable of fertilization. He prepared a sperm-free, hyaluronidase-containing filtrate from two million sperm. He then artificially inseminated rabbits (previously ovulated by means of chorionic gonadotrophin) with sperm concentrations known to be inadequate for fertility, but added to the semen the hyaluronidase-containing filtrate of sperm. In four out of five experiments the added hyaluronidase filtrate permitted fertilization to occur.

The observations of Rowlands, and McClean and Rowlands led us to apply their results to certain problems of human infertility. Is there a direct relationship between sperm concentration in man and the amount of hyaluronidase in semen? Do normal semen specimens, that is, normal as to sperm population (100 million or more

* Leonard and Kurzrok observed that the enzyme papain dispersed the follicle cells of the rat with equal rapidity, but at the same time seemed to damage the ovum.

per cc.), morphology, motility, etc., always contain hyaluronidase? Is the amount of hyaluronidase necessary to dissolve the gel about the follicular cells always the same, or do gels vary as to their content of hyaluronic acid? Do some sterile women exhibit antibodies to hyaluronidase? What are the best methods of utilizing hyaluronidase clinically? Can one utilize antibody formation against hyaluronidase as a method of inducing sterility? How is hyaluronidase transported by sperm? Is there a selective secretion of hyaluronidase by the Fallopian tubes? What is the effect of the menstrual cycle? Our observations give us only a partial answer to some of these problems and lead to speculation about the others.

## EXAMINATION OF SEMEN

Sterile glass containers are supplied and instructions given to collect the specimens in the morning and bring them to the office within two hours. Condom specimens are not accepted. The following is the routine procedure:

1. Measurement of semen volume.

2. Motility rating. Motility is estimated by the standards of Lambert and McKenzie (1940). A small drop of semen is placed on a slide with a cover glass and the specimen is observed at room temperature using a microscope with a magnification of 400 diameters. The motility observed is designated as 0, +1, +2, +3, +4 or +5. The +5 denotes maximum motility.

3. Percentage of motile spermatozoa. The percentage of motile spermatozoa is determined by covering a small drop of semen with a glass cover slip and examining it under the microscope at 400 diameters magnification after warming to body temperature. Several fields are examined and the percentage of motile sperm determined. Another method for determining the percentage of motility is the staining procedure of Hammen (1944) using brilliant cresyl blue and gum arabic. In this procedure the motile sperm will be colored blue-purple and the non-motile sperm will not be colored. We believe, however, that in view of the time (at least one hour) consumed in staining, the accuracy is not great enough to warrant its use routinely.

4. Percentage of abnormal spermatozoa. Using both × 400 magnification and oil immersion (× 1350), the percentage of cells that are not perfectly normal is estimated. The abnormalities include embryonal forms, angulated sperm, headless sperm, tailless sperm, sperm with misshaped heads, macro heads, micro heads, cytoplasmic collars, double headed sperm, double tailed, and pin-headed sperm. A fairly accurate determination can be made by counting the number of abnormal cells present in counts of 10 cells each, and averaging five such counts taken in different fields of the slide.

5. Concentration counts. The concentration of spermatozoa (number per cc.) was determined by means of a hemacytometer with a Neubauer counting chamber in the following manner: The semen is stirred with the white cell pipette and is then sucked into the pipette to the 0.5 mark, or to the 1 mark if the count on superficial examination appears to be low. The tip of the pipette is wiped and the diluting fluid is sucked up to the 11 mark. (For the diluting fluid use 5 cc. saturated $NaHCO_3$ to 95 cc. of 1 per cent formalin.) The pipette is shaken thoroughly. The counting is done in the same way that red blood cells are counted (i.e., 5 squares). The final figure is multiplied by 1,000,000 if the dilution is 1 to 20 (i.e., the semen was taken up to the 0.5 mark); or the final figure is multiplied by 500,000 if the dilution is 1 to 10 (i.e., the semen was taken up to the 1 mark).

6. Hyaluronidase assay. The method of determining hyaluronidase in semen is based

on the fact that a clot is formed when hyaluronic acid is combined with acidified serum proteins (blood serum). When hyaluronidase acts on the hyaluronic acid, however, the clot does not appear upon the subsequent addition of acidified blood. The hyaluronic acid is depolymerized and split by the enzyme into simpler products which do not give a precipitate or clot. If hyaluronic acid is layered carefully over acid serum, a distinct white ring will form immediately at the interface. In the presence of hyaluronidase a ring will not form, and the interphase as well as the layers will remain clear.

*I. Preparation of Buffers:*

Solution 1. *Acetic acid* 0.5*M*—30.015 Gm. $CH_3COOH$ made to a liter with distilled water.

Solution 2. *Sodium acetate*—68.035 Gm. $NaC_2H_3O_2.3H_2O$/liter distilled water.

Solution 3. *Acetate buffer* 0.1*M*; *pH*6.0—1 cc. solution 1 plus 20 cc. solution 2. Take 20 cc. of the mixture, dilute to 100 cc. with distilled water.

Solution 4. *Acetate buffer* 0.5*M*, *pH*4.2—28 cc. solution 1 plus 10 cc. solution 2.

*II. Preparation of Materials:*

1. *Substrate.* Na-hyaluronate 0.025 Gm. is completely wetted with two or three drops of glycerine, and is dissolved in 10 cc. of 0.1M acetate buffer at pH 6.0. The hyaluronic acid dissolves slowly, so constant stirring with a glass rod is necessary. This solution is kept in the ice-box until needed, at which time it is brought to room temperature. (1 cc. = 2.5 mg.)

2. *Enzyme.* Hyaluronidase 0.025 Gm. is dissolved in 10 cc. of 0.1*M* acetate buffer at pH 6.0. This solution should not be kept more than two to three hours.

3. *Acidified Serum.* 10 cc. of human blood collected anerobically,* is centrifuged after having been allowed to stand undisturbed for one-half hour. Five cc. of the clear serum is added to 45 cc. of 0.5*M* acetate buffer at pH 4.2. The serum is acidified to pH 3.1 with approximately 1.4 cc. of 4*M* HCl (Seastone, 1943).

4. *Semen.* One cc. of human semen, collected ¼ to five hours before use, is added to 0.1M acetate buffer at pH 6.0. The amount of acetate buffer added depends on the dilution of semen desired.

*III. Apparatus:*

1. *Micro-Boerner Centrifuge Filter.* The Boerner filter* is essential to the test. Semen is a turbid suspension and the ring cannot be seen unless the semen is filtered. In ordinary filtration methods there is a large percentage of loss when 1 cc. of the material is filtered. The Boerner filter is a modification of the Seitz filter, using centrifugal force instead of suction. It is composed of two parts: a base which holds the filter paper, and a cylinder which is screwed into the base (Boerner 1942).

2. *Layering Tube.* For the purpose of layering the solutions with the least amount of effort and disturbance we have found the following arrangement to be of great help. A 10 cc. centrifuge tube is held in an inclined position (about 35°) by a clamp attached to a ring-stand. The bottom of the centrifuge tube is packed with cotton to prevent breakage. It is advisable to put in sufficient cotton so when the Kahn tube is placed within the centrifuge tube the mouth of the Kahn tube protrudes slightly. This facilitates removal of the tube.

*IV. Procedure:*

1. One-half cc. of substrate (Na hyaluronate 1.25 mg.) is added to test tubes a, b, c, d, and e containing the following:

Tube a—1 cc. undiluted semen

Tube b—½ cc. undiluted semen

* For this procedure see: Peters, J. P. and Van Slyke, D. D. Quantitative Clinical Chemistry. Vol. II, chap. II. Baltimore, 1932. Williams & Wilkins Co.

* This filter and filter pads can be purchased from the Arthur H. Thomas Company, Philadelphia, Pennsylvania.

Tube c—½ cc. of the diluted semen (0.25 cc. semen plus 0.25 cc. acetate buffer pH 6.0)

Tube d—½ cc. buffer (0.1*M* acetate pH 6.0)

Tube e—1 cc. hyaluronidase solution

2. The contents of the test tubes a, b, c, d, and e are mixed with *separate* stirring rods and are placed in the incubator or water-bath at 37.5°c. for one hour.

3. The turbid solutions are filtered through micro-Boerner centrifuge filters into Kahn precipitation tubes at 2200 RPM for twenty-five minutes. The filtrate is clear and may contain hyaluronic acid or depolymerized hyaluronic acid, and the split products, but does not contain spermatozoa.

4. The Kahn tube containing the filtrate is placed in the layering tube. One cc. of the acidified serum is carefully layered on 1 cc. or less of the clear filtrate. If the specific gravity of the filtrate is not high enough to support the acidified serum, the procedure can be reversed, the filtrate being layered on the acidified serum. At the interface of the two liquids a white ring will appear *immediately* if hyaluronidase is absent or present in insufficient concentration. In the presence of sufficient hyaluronidase a ring will not be formed. Usually the ring (or mucin clot) will appear immediately. The ring will vary in intensity according to the amount of hyaluronic acid unacted upon by the enzyme. The greater the depolymerization the less the ring; with complete depolymerization there is no ring. Occasionally, the ring will not appear for sixty seconds. If the ring appears at the end of five to ten minutes and is faint in appearance, it implies that the amount of hyaluronidase is just about sufficient to depolymerize the available hyaluronic acid.

We have attempted to establish a hyaluronidase unit for semen, based on the action of a purified hyaluronidase on fairly pure hyaluronic acid. For purposes of convenience in handling, we chose a concentration of 2.5 mg. of hyaluronic acid per cc. as our substrate. The amount of the most highly purified enzyme preparation needed to depolymerize 2.5 mg. of hyaluronic acid was approximately 2.5 mg. It can be readily seen that such a unit would vary with the purity of both substances. We found that semen specimens containing 100 million sperm per cc. and which contained hyaluronidase, exhibited an activity sufficient to depolymerize 2.5 mg. of hyaluronic acid. Hence, our hyaluronidase unit for semen (H.U.S.) is that amount of enzyme in 1 cc. of semen sufficient to depolymerize 2.5 mg. of hyaluronic acid under the conditions of the experiment. If 2 cc. of semen are required to depolymerize 2.5 mg. of hyaluronic acid, the specimen contains 0.5 H.U.S. per cc. If 0.5 cc. of semen is required, the specimen contains 2 H.U.S. per cc. of semen. If the amount of semen is inadequate, we may use 0.5 cc. of semen acting upon 1.25 mg. of hyaluronic acid.

## COMMENTS

Table 1 represents a study of ninety semen specimens derived in the main from infertile couples. Four cases of repeated miscarriage are also included. The concentration of hyaluronidase in semen increases with the sperm population. This is also borne out by Graph A. This confirms the findings of Joël and Eichenberger (1945) and Werthessen et al. (1945). The critical point appears to be at 50 million sperm per cc. Below this level practically no hyaluronidase can be found in the semen, except in specimens Nos. 370, 438, 359 and 411. The concentration of hyaluronidase definitely increases as the sperm population exceeds 50 million per cc. It is interesting to correlate this fact with the clinical observation held for many years that specimens below a sperm concentration of 50 million per cc. have a very low fertility value.

TABLE I

| Series 1946 | | Sperm Concentration Million/cc. | H-ase Units | Motility | | Morphology Per Cent Abnormal | Approx. Age of Spec. Hr. | Clinical Notes |
|---|---|---|---|---|---|---|---|---|
| Case No. | Spec. No. | | | Degree | Per Cent Motile | | | |
| 1 | 341 | 0 | 0 | 0 | 0 | 0 | 1 | P. Entirely normal* |
| 2 | 346 | 0 | 0 | 0 | 0 | 0 | Office | P.† Wife not seen; injury to testes as child |
| 3 | 416 | 0 | 0 | 0 | 0 | 0 | 3 | P. Hypogonadism of husband |
| 4 | 435 | 0 | 0 | 0 | 0 | 0 | 3 | P. Gravid with previous husband but miscarried |
| 5 | 327 | 1 | 0 | 5 | 99 | 5 | Office | S.‡ Right cystic ovary study not complete; tubes patent under 120. Pruritus of scrotum—treated with *x*-ray |
| 6 | 339 | 1 | 0 | 5 | 50 | 40 | 1 | Same as case No. 5 |
| 7 | 401 | 1 | 0 | 5 | 85 | 30 | Office | P. Incomplete§ |
| 8 | 342 | 2 | 0 | 5 | 70 | 20 | Office | S. Mild genital hypoplasia, otherwise entirely normal |
| 9 | 379 | 2 | 0 | Oscillation | | 80 | 2½ | P. Biopsy normal, tubes closed |
| 10 | 334 | 3 | 0 | 4 | 15 | 30 | Office | P. Wife not seen |
| 11 | 373 | 4 | 0 | 5 | 10 | 90 | Office | P. Acute antiflexion of uterus, cervical and vaginal hypoplasia |
| 12 | 397 | 8 | 0 | 0 | 0 | 30 | Office | S. Repeated misc. (3); fundal hypoplasia |
| 13 | 360 | 10 | 0 | 5 | 70 | 30 | Office | Same as No. 8 |
| 14 | 438 | 13 | .17 | 3 | 30 | 35 | 3 | P. Incomplete |
| 15 | 365 | 15 | 0 | 4 | 30 | 50 | 2 | Same as No. 14 |
| 16 | 390 | 16 | 0 | 4 | 25 | 50 | 5 | S. Entirely normal |
| 17 | 395 | 20 | 0 | 4 | 20 | 70 | 4½ | Same as No. 11 |
| 18 | 357 | 25 | 0 | 5 | 45 | 15 | 2 | S. Entirely normal |
| 19 | 359 | 25 | .38 | 4 | 30 | 25 | 3 | S. Prolongs estrogen phase, inadequate luteinization, hypothyroidism |
| 20 | 411 | 25 | .17 | 4 | 50 | 35 | 2 | S. Repeated miscarriage fundal hypoplasia |
| 21 | 326 | 30 | 0 | 5 | 35 | 70 | 1½ | P. Tubes patent at 180 otherwise entirely normal |
| 22 | 404 | 30 | 0 | 5 | 25 | 25 | 2 | S. Small fibroid otherwise normal |
| 23 | 344 | 31 | 0 | 5 | 80 | 20 | 1 | P. Genital hypoplasia, progestational endometrium with cystic tendency otherwise normal |
| 24 | 370 | 36 | .75 | 5 | 25 | 25 | Office | P. Mild genital hypoplasia |
| 25 | 432 | 38 | 0 | 0 | 0 | 50 | 2 | P. Incomplete |
| 26 | 362 | 40 | 0 | 2 | 20 | 50 | 3 | P. Genital hypoplasia |
| 27 | 340 | 41 | 0 | 5 | 45 | 40 | 2½ | Same as No. 19 |
| 28 | 391 | 42 | 0 | 5 | 70 | 35 | 1 | P. Mild genital hypoplasia, tubes patent with antispasmodic |
| 29 | 355 | 42 | 0 | 4 | 30 | 60 | 5 | P. Congenital retroversion, cervical hypoplasia |
| 30 | 394 | 43 | 0 | 4 | 30 | 45 | 5 | Same as No. 26 |
| 31 | Pl. 4-23 | 45 | 0 | 4 | 40 | 50 | 2 | P. Mild fundal hypoplasia |
| 32 | 332 | 45 | 0 | 3 | 40 | 50 | 5 | S. Mobile retroversion, otherwise normal |
| 33 | 331 | 50 | 2 | 3 | 35 | 65 | 3½ | S. Now gravid |
| 34 | 429 | 51 | .38 | 5 | 90 | 5 | 2½ | P. Small intramural fibroid |
| 35 | 353 | 51 | 0 | 4 | 50 | 45 | 2½ | P. Entirely normal |
| 36 | 372 | 55 | >1 | 4 | 40 | 30 | Office | P. Entirely normal |
| 37 | 437 | 55 | >67 | 5 | 75 | 20 | 23 | P. Entirely normal |
| 38 | 357 | 57 | .5 | 5 | 50 | 20 | 2 | P. Right salpingo-oophorectomy; partial resection of left ovary remaining tube patent at high pressure |

TABLE I—(*Continued*)

| Series 1946 | | Sperm Concentration Million/cc. | H-ase Units | Motility | | Morphology Per Cent Abnormal | Approx. Age of Spec. Hr. | Clinical Notes |
|---|---|---|---|---|---|---|---|---|
| Case No. | Spec. No. | | | Degree | Per Cent Motile | | | |
| 39 | 415 | 59 | 0 | 4 | 50 | 40 | 2 | P. Genital hypoplasia; incomplete |
| 40 | 413 | 63 | .75 | 5 | 50 | 20 | 3½ | Same as No. 29 |
| 41 | 352 | 64 | .75 | Oscillation | | 30 | 1½ | S. Hypertension, pituitary adiposity |
| 42 | 371 | 65 | >1 | 5 | 75 | 25 | 2½ | P. Genital hypoplasia; fibroid uterus, tubes patent at 170 mm. |
| 43 | 399 | 67 | .75 | 5 | 65 | 25 | 2½ | S. Entirely normal |
| 44 | 398 | 69 | .75 | 5 | 60 | 30 | 2½ | P. Cervical hypoplasia |
| 45 | K5–7 | 70 | 0 | 4 | 85 | 20 | 4 | P. Entirely normal |
| 46 | 364 | 73 | >1 | 4 | 60 | 40 | 3 | P. Tubes closed |
| 47 | 374 | 74 | .75 | 5 | 70 | 30 | 2 | P. Genital hypoplasia |
| 48 | 418 | 75 | 0 | 5 | 85 | 30 | 3 | S. Completely normal |
| 49 | 367 | 76 | .38 | 5 | 50 | 30 | 3 | P. Genital hypoplasia, old parametritis |
| 50 | 386 | 80 | .83 | 3 | 30 | 65 | 2½ | P. Uterine fibroids; inadequate lutein phase |
| 51 | 366 | 85 | 0 | 5 | 85 | 30 | 1½ | P. Tubes patent, old pelvic inflammatory disease |
| 52 | 361 | 88 | 1 | 5 | 90 | 20 | 1 | P. Entirely normal |
| 53 | 392 | 93 | 0 | 5 | 85 | 25 | Office | P. Cervical hypoplasia |
| 54 | 356 | 95 | 0 | 3 | 25 | 55 | 5½ | Same as No. 33 |
| 55 | 406 | 100 | .5 | 5 | 60 | 35 | 1 | P. Entirely normal |
| 56 | 389 | 101 | 1.5 | 5 | 60 | 20 | 2 | P. Entirely normal |
| 57 | 431 | 101 | >1 | 5 | 40 | 60 | 3 | P. Tubes patent, incomplete |
| 58 | 333 | 101 | 2 | 5 | 85 | 30 | Office | P. Cervical hypoplasia; acquired retroversion |
| 59 | 427 | 110 | >1 | 5 | 50 | 30 | 3 | Same as No. 39 |
| 60 | PE. 3–29 | 100† | >3 | 5 | 85 | 20 | 3 | P. Entirely normal |
| 61 | 424 | 112 | 1 | 3 | 35 | 35 | 4 | P. Entirely normal |
| 62 | 380 | 123 | .75 | 5 | 25 | 35 | 2½ | P. Moderate sec. endometrium |
| 63 | 428 | 133 | .75 | 5 | 85 | 15 | 3 | P. Incomplete |
| 64 | 422 | 133 | .80 | 5 | 85 | 10 | 2½ | S. Incomplete |
| 65 | MA. 4-22 | 134 | 0 | 5 | 95 | 10 | 3 | Donor |
| 66 | 325 | 136 | >1 | 4 | 85 | 20 | 3 | S. Repeated misc. (3); moderate genital hypoplasia, otherwise normal |
| 67 | MA 64 | 137 | .38 | 5 | 90 | 10 | 22 | Same as No. 65 |
| 68 | 377 | 146 | 0 | 5 | 65 | 20 | 3½ | Same as No. 35 |
| 69 | 354 | 146 | >3 | 5 | 80 | 30 | 1½ | P. Incomplete |
| 70 | 387 | 155 | 1.25 | 5 | 85 | 20 | Office | S. Pituitary adiposity, hypertension |
| 71 | 414 | 155 | 0 | 5 | 75 | 25 | 2½ | S. Entirely normal |
| 72 | MA 4-3 | 157 | 0 | 5 | 85 | 10 | 3 | Same as No. 65 |
| 73 | MAR 4-4 | 158 | >2 | 5 | 85 | 25 | 3½ | Same as No. 58 |
| 74 | MA 5-1 | 160 | >.4 | 5 | 85 | 10 | 4 | Same as No. 65 |
| 75 | 375 | 164 | >1 | 5 | 50 | 20 | 1½ | P. Inadequate secretory endometrium |
| 76 | 385 | 170 | 1.5 | 5 | 85 | 15 | 1½ | P. Small fibroid |
| 77 | 434 | 177 | >3 | 5 | 90 | 10 | 2 | P. Entirely normal |
| 78 | 417 | 187 | 0 | 5 | 80 | 40 | 2 | P. Anovulatory cycle |

TABLE I—(*Continued*)

| Series 1946 | | Sperm Concentration Million/cc. | H-ase Units | Motility | | Morphology Per Cent Abnormal | Approx. Age of Spec. Hr. | Clinical Notes |
|---|---|---|---|---|---|---|---|---|
| Case No. | Spec. No. | | | Degree | Per Cent Motile | | | |
| 79 | 396 | 193 | 0 | 5 | 85 | 15 | 5 | S. Repeated misc. (3); vaginal and cervical hypoplasia; incomplete |
| 80 | 368 | 200 | >2 | 5 | 50 | 60 | Office | P. Genital hypoplasia |
| 81 | 433 | 201 | 0 | 5 | 80 | 80 | 3 | S. Incomplete |
| 82 | 345 | 205 | >10 | 5 | 50 | 30 | 3 | S. Entirely normal |
| 83 | 430 | 220 | >2 | 5 | 80 | 30 | 3¾ | P. Incomplete |
| 84 | 436 | 281 | >3 | 5 | 85 | 20 | 3 | P. Incomplete |
| 85 | 335 | 302 | >1 | 5 | 30 | 80 | Office | P. Tubes closed, otherwise normal |
| 86 | 343 | 310 | >10 | 5 | 65 | 35 | 2¾ | S. Thin proliferative endometrium; incomplete |
| 87 | 369 | 332 | 2.5 | 4 | 90 | 30 | 2½ | S. Repeated misc. (5); cervical hypoplasia, congenital retroversion |
| 88 | F. | 363 | >2 | 5 | 90 | 10 | Office | Control |
| 89 | 378 | 410 | 1.25 | 4 | 40 | 40 | 3 | Same as No. 85 |
| 90 | F. | 468 | 2.2 | 5 | 90 | 10 | Office | Control; same as No. 88 |

* By entirely normal we mean physical examination negative, pelvis negative, tubes patent at pressure under 140 mm. Hg., patient ovulates, endometrium good secretory phase, basal metabolism rate normal.

† Primary sterility.

‡ S. Secondary sterility.

§ By incomplete we mean that the patient has not been completely studied. Plus 5 indicates maximum motility.

Specimens with large concentrations of sperm do not of necessity have great concentrations of hyaluronidase, so that in specimens having a sperm population greater than 100 million per cc. there is no direct relationship between concentration of sperm and the amount of hyaluronidase. Patient F. (case 88) produced 362 million sperm per cc. containing > 2 H.U. in his first specimen, and 468 million sperm per cc. and 2.2 H.U. in a subsequent specimen.

Table 1 exhibits several interesting points. Two cases present concentrations of sperm between 90 and 100 million per cc. One would have expected to find hyaluronidase in these specimens. None was found. Specimen No. 277 (case 68) with 146 million sperm per cc. having excellent percentage motility and motility, and fairly good morphology, would ordinarily be considered a good specimen. Yet it contained no hyaluronidase. The same situation occurs in specimen No. 414 (case 71). Hence the fact that a specimen has an adequate and even a very large sperm population does not always imply that hyaluronidase is present in the semen, and, from our present viewpoint, that it is fertile.

There appears to be no relationship between the amount of hyaluronidase and (1) sperm morphology, (2) percentage of motile sperm, and (3) motility of sperm.

Several cases listed in this group illustrate a number of interesting points. Patient Mac, a young man of robust health, has been used as a donor in cases of artificial insemination for the past three years. He was the most successful of the donors. Early in 1945 the percentage of pregnancies induced by him was reduced to zero, whereas it had formerly been 66 per cent. His semen specimen showed no demonstrable change. It was excellent according to all criteria used for evaluation of a specimen (sperm concentration, morphology, motility, semen-mucus penetration, etc.). In view of the fact that we were then working with hyaluronidase, we added

10 mg. of the enzyme to each specimen and then inseminated. We have obtained nine pregnancies since. We therefore examined his specimens for hyaluronidase during the past four months with the following results:

TABLE II

| | Sperm Concentration, Million per Cc. | Hyaluronidase Units |
|---|---|---|
| March, 1946 | 134 | 0 |
| April, 1946 | 157 | 0 |
| May, 1946 | 160 | > .4 |
| June, 1946 | 137 | .38 |

Our assumption that his specimen lacked hyaluronidase, and because of that was of low fertility, was justified by an immediate increase in the number of pregnancies upon the addition of the enzyme to his specimen, and by the actual demonstration of the absence of hyaluronidase in his semen.

Another interesting case is case 79 (spec. No. 396). The problem here is one of three repeated miscarriages. We believe that they were due to a cervical hypoplasia (Kurzrok 1946). In spite of a sperm concentration of 193 million per cc. there is no hyaluronidase in the specimen. Whether this factor is related to the problem of repeated miscarriage we do not know. A second case of three repeated miscarriage is case 12 (No. 397). Here the sperm concentration is 8 million per cc., hence the absence of hyaluronidase is to be expected. A further interesting relationship is borne out by the following cases: Case 35 (No. 353) exhibited 51 million sperm per cc. and no hyaluronidase. A second specimen gave 146 million per cc. also without enzyme. On the other hand, case 39 (No. 415) produced 59 million sperm without hyaluronidase, and a second specimen one week later 110 million sperm per cc. containing 1 H.U.S.

We are now treating patients that are sterile because of inadequate semen specimens by the therapeutic administration of hyaluronidase. The cases chosen for treatment are those in which defective semen is the sole cause of sterility. All other factors and tests are normal. Of course, other criteria that are used in judging the adequacy of semen specimens, aside from sperm concentration, such as morphology, percentage of sperm motility, degree of motility, semen-mucus penetration, must not be overlooked.

We have utilized hyaluronidase in two ways:

1. *By Direct Addition to the Specimen.* The patient brings the semen specimen to the office, or the specimen is produced in the office. The latter is preferable but not always feasible. Ten to 20 mg. of hyaluronidase are added to the specimen and thoroughly stirred. The enzyme goes into solution. The enzyme does not modify the motility of the spermatozoa nor does it liquify cervical mucus, a fact previously recorded by Rowlands. The specimen is then taken up into a syringe and the cervix is sprayed. The semen is never injected into the uterine cavity. Immediately after insemination the patient is put into a steep Trendelenburg position for twenty minutes. The date chosen for the insemination is the date of ovulation as previously determined by the method of Papanicolaou and Shorr, or by such clinical signs of ovulation that may be present. Where the insemination is carried out more than once during a given cycle we inseminate two days before and after ovulation. We have never noted any allergic or pathologic phenomena from the use of hyaluronidase. The same technic was utilized in artificial insemination with an outside donor.

2. *By Direct Application to the Cervix.* In view of the fact that it is not always feasible for the patient to bring semen specimens to the office on specified dates of the cycle we utilized the second method, namely, the

direct application of hyaluronidase to the cervix. The patient came to the office on the date of ovulation or as near to that date as possible. The cervix was exposed by means of a speculum and the surface of the cervix (but not the canal) was wiped clean. Ten mg. of hyaluronidase was then placed in a sterile watch glass. A sterile cotton applicator was inserted into the mucus of the cervical canal. By twisting the applicator in the canal small amounts of mucus will cling to the cotton. The applicator is then dipped into the enzyme which clings to the mucus, and inserted into the cervical canal. This is repeated several times until all enzyme is packed into the cervical canal. It is important not to cause bleeding from the cervical canal as it may wash out the enzyme or possibly inhibit its activity (Leonard and Kurzrok, 1946). The patient is then instructed to have coitus within the next few hours. This procedure is occasionally carried out three times during the cycle, two days before, during, and two days after the calculated day of ovulation.

The following cases of sterility illustrate the therapeutic use of hyaluronidase:

## CASE REPORTS

CASE J. S. The patient was twenty-six years of age. She was referred to us by Dr. George Urbach. The chief complaint was a primary sterility of four years' duration. Her menses were regular and the general physical examination was negative. Pelvic examination revealed a mild cervical hypoplasia.

Insufflation on September 27, 1945, showed the tubes to be closed at a pressure of 180 mm. of Hg. The patient was advised to take Trasentine. *

* It is our custom not to make a diagnosis of closed tubes on the basis of a single test even though the pressure is run up to 180 mm. on three successive tries. Beginning with the onset of the next menstrual period the patient is advised to take six tablets of Trasentine, each 75 mg. per day, up to the mid-cycle when insufflation is again carried out. More than 50 per cent of the patients with previously closed tubes now show normal tubal patency. We believe the closure to have been due to tubal spasm. We are indebted to the late Mr. Robert Mautner of Ciba Corp. for the Trasentine.

On October 2, 1945, the insufflation test was repeated. The pressure rose to 180 mm. and dropped to 80 mm., gas passed through. Typical shoulder symptoms developed thereby implying that the tubes were patent.

On November 2, 1945, an endometrial biopsy revealed a good secretory endometrium, slightly cystic. Ovulation (Papanicolaou and Shorr) occurred on the thirteenth day of the cycle.

A semen examination on August 22, 1945, gave the following results:

Semen #P77. Age—2 hr. Volume 1 cc.
Viscosity—mucoid.
Motility—30 to 40 per cent motile. Some oscillatory motion.
Morphology—70 to 75 per cent abnormal.
Count—19 million per cc.

Another semen examination on September 21, 1946, revealed the following:

Semen #P99. Age—2 hr. Volume 2 cc.
Viscosity—mucoid.
Motility—40 per cent motile. Oscillatory motion.
Morphology—70 to 75 per cent abnormal. Granular and cellular débris.
Count—19 million per cc.

The patient was in to see me on December 10, 1945. Her last menstrual period was November 29, 1945. This was on the twelfth day of the cycle. Ten mg. of hyaluronidase was applied to the cervix and the patient instructed to have intercourse within a few hours.

The A-Z test was positive on January 10, 1946.

CASE A. W. M. The patient was thirty-one years of age. The chief complaint was a secondary sterility of seven years' duration. She conceived immediately in 1938, miscarried at three months and then had a D and C. Her menses were regular; the general physical examination was negative. The pelvic examination showed a moderate genital hypoplasia.

On October 26, 1945, an insufflation test showed the tubes to be closed at 180 mm. of Hg. The patient was advised to take Trasentine.

On November 5, 1945, an endometrial biopsy revealed a secretory endometrium. Ovulation occurred on the fifteenth day of the cycle.

An insufflation on December 13, 1945, showed the tubes patent at 180 mm. of Hg. Typical shoulder symptoms developed. The patient was advised to take Trasentine.

On February 5, 1946, insufflation test showed tubes patent at 140 to 120 mm. of Hg. Typical shoulder symptoms developed.

The patient came in to the office on March 6, 1946. Her last menstrual period was February 22, 1946. Hyaluronidase was applied to the cervix, and she was given an injection of 2,000 R. U. Progynon B.

The patient was in again on March 27, 1946. Her last menstrual period was March 21, 1946. Hyaluronidase was applied to the cervix, and she was given an injection of 1,000 I.U. Anteron (equine gonadotrophin). The purpose of the injection was to hasten the date of ovulation, for the patient had made this visit somewhat too early in the cycle. She was advised to have intercourse within a few hours. The patient brought in a semen specimen collected two hours before her arrival at the office. Coitus was advised again on the same day even though a second semen specimen produced during the same day is apt to be of poorer quality when compared with the first.

A semen examination on October 26, 1945, gave the following results:

Semen #P142. Age—2 hr. Volume 2 cc.
Viscosity—normal.
Motility—5 per cent, plus 1.
Morphology—65 to 70 per cent abnormal. Many embryonal forms, headless sperm, cellular débris.
Count—19 million per cc.

Another semen examination on March 27, 1946, showed the following:

Semen #P324. Age 2 hr. Volume 1.5 cc.
Viscosity—very viscous.
Motility—60 per cent motile, plus 5.
Morphology—35 per cent abnormal. Cytoplastic residues, headless forms.
Count—128 million per cc.

On May 4, 1946 the A-Z test was positive.

The patient then brought in another specimen after she conceived. The purpose of obtaining this specimen was to determine its hyaluronidase content, for we had previously assumed without testing that none was present. Our assumption was correct for the specimen did not contain hyaluronidase. The specimen brought in on May 20, 1946, gave the following results:

Semen #P418. Age 3 hr. Volume 1 cc.
Viscosity—viscous.
Motility—85 per cent, plus 5.
Morphology—30 per cent abnormal, misshaped heads, embryonal forms.
Count—75 million per cc.
Hyaluronidase—none present, (lowest amount tested 0.75 H.U.).

Case K. K. The patient was twenty-nine years of age. She was referred to us by Dr. W. Phelan. The chief complaint was a secondary sterility of one year's duration. She conceived three years before and had a normal delivery. Her menses have been normal, and the general physical examination was negative. The pelvic examination showed a first degree retroversion, mobile.

On March 20, 1945, an insufflation showed the tubes to be patent at 160 to 90 mm. of Hg. Typical shoulder symptoms developed.

On March 28, 1945, an endometrial biopsy revealed a secretory endometrium. Ovulation occurred on the eleventh or sixteenth day of the cycle. The vaginal spreads were not quite clear.

An insufflation on May 9, 1945, showed the tubes patent at 90 to 60 mm. of Hg. Typical shoulder symptoms developed.

A semen test on March 29, 1945, showed the following results:

Semen. Age 2½ hr. Volume 2 cc.
Viscosity—normal.
Motility—75 per cent motile. Plus 4.
Morphology 75 per cent abnormal, embryonal forms.
Count—20 million per cc.

A semen examination on November 8, 1945, gave the following results:

Semen #P160. Age 2 hr. Volume 2.5 cc.
Viscosity—normal.
Motility—plus 1.
Morphology—75 per cent abnormal.
Count—107 million per cc.

Another semen examination on February 4, 1946, gave the following results:

Semen #P 252. Age 2.5 hr. Volume 4 cc.
Viscosity—normal.
Motility—0.
Morphology—65 per cent abnormal, embryonal forms.
Count—196 million per cc.

In view of the repeated poor motility the patient was seen by Dr. Irving Lerman within two hours after coitus; motile sperm were found in the vagina and cervix.

On March 16, 1946, the patient came to the office. Her last menstrual period was March 6, 1946. Hyaluronidase was applied to the cervix.

On April 29, 1946, the A-Z test was positive.

Case M. S. The patient was twenty-six years of age. The chief complaint was primary sterility of four years' duration. The patient has had two previous complete studies made of her problem and all findings were normal. Studies were repeated again for verification. Physical and pelvic examinations were negative.

On February 12, 1946, an insufflation showed the tubes to be patent at 70 mm. of Hg. On March 20, 1946, endometrial biopsy revealed a secretory endometrium. On April 5, 1946, the patient was seen by me. Her last menstrual period was March 24, 1946. Hyaluronidase was packed into the cervix.

The patient came in to see me on May 23, 1946. Examination showed her to be pregnant as she had missed her April period.

A semen examination on February 12, 1946, gave the following results:

Semen #P261. Volume 3.5 cc.
Viscosity—normal.
Motility—85 per cent motile, plus 5.
Morphology—10 per cent abnormal.
Count—392 million per cc.

Case F. J. The patient was thirty-four years of age. The chief complaint was primary sterility of four years' duration. Her menses had been regular, but she had a menstrual migraine. Previous insufflations revealed patent tubes. The genera! physical examination was negative. She had been taking thyroid gr. ¼ to to ¾ per day, also hormone injections. The pelvic examination showed mild genital hypoplasia and a congenital retroversion.

A basal metabolism test on January 23, 1946, gave a minus 11 per cent result. The thyroid was increased to gr. 1 per day.

On January 23, 1946 a semen examination gave the following results:

Semen #P 230. Age 2 hr. Volume 2.0 cc.
Viscosity—normal.
Motility—35 per cent motile, 3 plus.
Morphology—60 per cent abnormal, embryonal forms.
Count—112 million per cc.

On February 7, 1946, an endometrial biopsy revealed a secretory endometrium. Ovulation occurred on the fifteenth day of the cycle.

The patient was in to see me on March 28, 1946. Her last menstrual period was March 18, 1946. She was given 1,000 I.U. Anteron (equine gonadotrophin), and 500 I.U. Follutein (chorionic gonadotrophin) to hasten ovulation. Hyaluronidase was packed into the cervix.

On April 25, 1946, the patient came into see me. Her last menstrual period was April 15, 1946. She was given 800 I.U. Anteron and 500 I.U. Follutein. Hyaluronidase was packed into the cervix.

On May 27, 1946, the A-Z test was positive.

Case E. H. The patient was thirty years of age. The chief complaint was primary sterility four years' duration. The patient had had several previous examinations and numerous tests. The physical examination showed acute anteflexion of the cervix, and a cervical hypoplasia. Tubes were previously found patent, therefore an insufflation was not done.

On March 26, 1946, endometrial biopsy revealed a moderate secretory endometrium. Ovulation occurred on the twelfth day of the cycle. The slides also showed a prolonged estrogen phase.

A semen examination on March 15, 1946, showed the following findings:

Semen #P305. Age 2½ hr. Volume 2 cc.
Viscosity—slight.
Motility—25 per cent motile, plus 3, plus 2.
Morphology—50 per cent abnormal, embryonal forms, angulated.
Count—67,000,000.

On April 6, 1946, a semen examination gave the following results:

Semen #P336. Age 2½ hr. Volume 3 cc.
Viscosity—normal.
Motility—70 per cent motile, plus 5.
Morphology—15 per cent abnormal, angulated heads.
Count—181,000,000.

The patient came to see me on May 2, 1946. Her last menstrual period was April 21, 1946. Hyaluronidase was packed into the cervix.

On June 3, 1946, the A-Z test was positive.

One of the problems posed by these cases is the manner by which the added hyaluronidase reaches the ovum. The answer to this problem would involve the correct explanation for the mode of transport of sperm from the vagina into the tubes in the human. The simplest explanation of the latter phenomenon is that the sperm reach the ends of the tubes by their own motility. The added hyaluronidase could be absorbed on the surface of the sperm and thus reach the ovum. A second explanation offered for the sperm transport is that sperm are aspirated into the uterus and tubes by the muscular action of these organs. Hyaluronidase could be transported in the same manner. Somehow this explanation has never been accepted by gynecologists. The senior writer has conducted experiments with the human uterus both *in vivo* and *in vitro* over a period of many years and has never noted any physiological action of the uterus that would imply aspiration.

There are two other explanations that might be offered for the manner in which hyaluronidase could reach the ovum within the tube. One is absorption of the enzyme by the cervical mucosa and its selective secretion by the secreting cells in the tubal mucosa. Rosenzweig and Walzer (1943) have shown that peanut protein entered the circulation in from eight to twenty-five minutes after its application to the cervix. The cervical mucous membrane is made up of columnar secreting epithelium, is rich in lymphatics and is covered with an alkaline secretion. Such factors favor absorption. Against this view is the inhibitory action of blood serum and possible antibody formation.

The fourth possible explanation for the concentration of hyaluronidase about the ovum is the following. Hyaluronidase carried to the ovum by the sperm initiates by its degradation of hyaluronic acid a further production of enzyme, possibly by the end products produced in this enzymatic reaction. The point of action of this initiating process may be the secretory cells of the tubal epithelium. It is worth commenting that no satisfactory explanation has been offered as to the function of these cells, except the generalized explanation that they aid in the nutrition of the ovum.

The form or manner by which hyaluronidase is held in semen is at present unknown. Is there a "bound" and a "free" hyaluronidase? Some insight into this problem is given by the following experiment. If a given semen contains no hyaluronidase, how much enzyme must be added to the semen for the latter to depolymerize a given amount of hyaluronic acid? Enzyme preparation No. 13-1811 required 2.5 mg. to depolymerize 2.5 mg. of hyaluronic acid (1 H.U.).

TABLE III

| Patient | Hyaluronidase Added, Mg. | Semen, Cc. | Amount of Hyaluronic Acid, Mg. | Result |
|---|---|---|---|---|
| S. | 2.5 | 1 | 2.5 | Ring in 10 min. |
| B. | 7.6 | 1 | 2.5 | Ring |
| F. | 12.0 | 1 | 2.5 | No ring |
| | 4.2 | 1 | 2.5 | No ring |
| Gr. | 3.4 | .4 | 2.5 | Ring |
| | 6.0 | .4 | 2.5 | Ring |
| | 7.8 | .4 | 2.5 | Ring |

These patients had no hyaluronidase in the semen. The addition of 4.2 mg. of enzyme was sufficient to demonstrate its activity in patient F., but the addition of 7.6 mg. to semen B failed to alter the original zero titer of enzyme. Either the enzyme was neutralized by some inhibitor (heparin inhibits the action of hyaluronidase on the rat ovum, Leonard and Kurzrok unpublished) or the enzyme entered a bound state from which it was not liberated by the conditions of the experiment. In view of these findings, we are not as yet in a position to state the precise quantity of hyaluronidase that should be added to a given semen specimen. The senior author has usually added 10 mg. and occasionally 20 mg., but even the latter amount may occasionally be insufficient.

It is an interesting theoretical consideration as to what should be the order of magnitude of sperm concentration about the ovum to yield sufficient hyaluronidase to liquefy the gel around the granulosa cells and ovum. Leonard and Kurzrok (unpublished) found that with the purest preparation of hyaluronidase available, 33 gamma of enzyme were necessary in order to disperse the follicle cells completely in the rat *in vitro* under standard conditions. If we accept the theoretical possibility that the amount of hyaluronidase necessary to disperse the follicle cells around the human ovum is in proportion, then we begin to gain some insight into the necessity for the production of such a large number of sperm in a single ejaculation. (Diameter of rat ovum 70–75 micra, human $130/140$ micra. Hartman 1929.)

According to some of our published data spermatozoa represent 160 mg. of wet weight per cc. of spermatic fluid containing 100 million sperm. One cc. of spermatic fluid weighs on the average 1.008 Gm. Hence a single sperm under these conditions weighs .0016 gamma. If the sperm were made entirely of hyaluronidase, it would require approximately 20,000 sperm to furnish 33 gamma of enzyme. If, for purposes of discussion, we assume that hyaluronidase represents only $1/1000$ of the weight of a sperm, it would follow that the ovum must be surrounded by at least 20 million sperm in order to produce an amount of hyaluronidase necessary for complete dispersal of the follicle cells. Such an assumption might explain why an ejaculate averaging 4 cc. must of necessity have better than 400 million sperm to be considered adequate. This figure is in agreement with the one derived by actual measurement of the amount of hyaluronidase in human semen and again indicates that specimens having less than 50 million sperm per cc. have a very low fertility value. The loss of sperm in their journey through the genital tract towards the ovum must also be taken into consideration.

The problem of antibodies against hyaluronidase can be considered as part of the greater problem of sperm immunity. Numerous papers have appeared in the past two years dealing with immunization against spermatic fluid and the resultant production of temporary sterility. Considerable discussion as to the validity of the results obtained, the specific antigens, and the implications of the results, has not led to further clarification of the problem. In a previous paper (Leonard and Kurzrok, 1946) we reported attempts to find inhibitory substances against bull hyaluronidase in nine sterile women. No such inhibitor was found. To determine if some types of sterility in women might be due to increased amounts of a normal or induced inhibitor (antibody to human sperm hyaluronidase) it would appear, in the light of our experiments, that hyaluronidase derived from human testis should be employed.

## CONCLUSIONS

1. A simple test for hyaluronidase in human semen has been described. It is

based on the fact that when hyaluronic acid is added to acidified blood serum a ring forms. In the presence of hyaluronidase a ring will not form. Clear seminal plasma, obtained by means of the Boerner centrifugal filter, is essential.

2. The hyaluronidase content of human semen, as studied in ninety specimens, increases directly with the sperm concentration up to the range of 100 million sperm per cc. Beyond this concentration the hyaluronidase content does not increase proportionately.

3. Semen specimens with excellent concentrations of sperm may not contain any hyaluronidase. We consider such specimens infertile.

4. The hyaluronidase content of semen does not appear to be related to sperm morphology, motility or percentage of motility.

5. A method is proposed for utilizing bull hyaluronidase in the treatment of sterility. The enzyme is added directly to the semen specimen and then utilized for artificial insemination, or is packed into the cervix and followed by normal coitus. Six cases so treated are described in some detail.

6. The concentration of sperm and hyaluronidase about the tubal ovum is discussed. From a theoretical viewpoint the hyaluronidase content of 20 million sperm is necessary for follicle dispersal. This is in accord with the high concentration of sperm present in the normal ejaculate, and the amount considered clinically as sufficient to be considered fertile.

7. An attempt to demonstrate antibodies (or inhibitors) against bull hyaluronidase in the blood serum of sterile women was not successful.

We are indebted to Dr. Karl Meyer for his many fruitful suggestions and his kind interest in this work. The bull testis hyaluronidase preparation was provided through the courtesy of Dr. Erwin Schwenk of the Schering Corporation, Bloomfield, N. J. The authors wish to extend their thanks to Miss Abigail K. Wright whose skill in the care of our patients made the clinical work possible; and additional thanks are due to Miss Phyllis Ruth Epstein and Mr. Matthew Conrad for their technical assistance.

## REFERENCES

1. Bacharach, A. L., Chance, M. R. A. and Middleton, T. R. *Biochem. J.*, 34: 1464–71, 1940.
2. Boerner, F. *Am. J. Clin. Path.*, 12: 68, 1942.
3. Boyand, F. and McClean, D. *J. Path. Bact.*, 41: 553–65, 1935.
4. Chain, E. and Duthie, E. S. *Nature*, 144: 977–78, 1939.
5. Chain, E. and Duthie, E. S. *Brit. J. Exper. Path.*, 21: 324–38, 1940.
6. Claude, A. *J. Exper. Med.*, 66: 353–66, 1937.
7. Duran-Reynals, F. *J. Exper. Biol.*, 58: 161–81, 1933.
8. Duran-Reynals, F. *J. Exper. Med.*, 69: 69–81, 1939.
9. Duran-Reynals, F. and Stewart, F. W. *Am. J. Cancer*, 15: 2790–97, 1931.
10. Fekete, E. and Duran-Reynals, F. *Proc. Soc. Exper. Biol. & Med.*, 52: 119–21. 1943.
11. Hamman, R. *Acta obst. et gynec. Scandinav.*, 24: 95–105, 1944.
12. Hartman, C. G. *Quart. Rev. Biol.*, 4: 373, 1929.
13. Hoffman, D. C. and Duran-Reynals, F. *Science*, 72: 508, 1930.
14. Humphrey, J. N. *Biochem. J.*, 37: 177–81, 1943.
15. Joel, C. A. and Eichenberger, E. *Schweiz. med. Wchnschr.*, 75: 601–604, 1945.
16. Kurzrok, R. *New York State J. Med.*, 56: 493–497, 1946.
17. Lambert, W. V. and McKenzie, F. F. *U. S. Dept. Agric. Circ.*, No. 567, 1940.
18. Leonard, S. L. and Kurzrok, R. *Endocrinol.*, 37: 171–176, 1945.
19. Leonard, S. L. and Kurzrok, R. *Endocrinol.*, (in press).
20. Lythgoe, B. and Madinaveitia, J. *Biochem. J.*, 37: 6–9, 1943.
21. Mann, T. and Lutwak-Mann, C. *Ann. Rev. Biochem.*, 13: 25–58, 1944.
22. McClean, D. *J. Path. Bact.*, 33: 1045–1070, 1940.
23. McClean, D. *J. Path. Bact.*, 42: 477–512, 1936.
24. McClean, D. *J. Path. Bact.*, 54: 284–86, 1942.
25. McClean, D. *Biochem. J.*, 37: 169–77, 1943.
26. McClean, D. and Rowlands, J. W. *Nature*, 150: 627, 1942.
27. Meyer, K. Cold Spring Harbor Symposia. *Quart. Rev. Biol.*, 6: 91–102, 1938.
28. Meyer, K. Advances in Protein Chemistry. Vol. II, p. 249. New York, 1945. Academic Press.
29. Meyer, K. and Palmer, J. W. *J. Biol. Chem.*, 107: 629–34, 1934.
30. Meyer, K. and Palmer, J. W. *Am. J. Ophth.*, 19: 859–865, 1936.
31. Papanicolaou, G. M. and Shorr, E. *Am. J. Obst. & Gynec.*, 31: 806, 1936.
32. Rosenzweig, M. and Walzer, M. *Am. J. Obst. & Gynec.*, 45: 286, 1943.
33. Rowlands, I. W. *Nature*, 154: 332, 1944.
34. Seastone, C. V. *J. Exper. Med.*, 77: 21, 1943.
35. Werthessen, N. T., Berman, S., Greenberg, B. E. and Gargill, S. L. *Am. J. Urol.*, 54: 565, 1945.

# Reviews

## Pneumonia*

### *Etiology, Diagnosis and Specific Treatment*

MAXWELL FINLAND, M.D.
BOSTON, MASSACHUSETTS

PNEUMONIA can no longer be considered as a single disease entity, but rather we must think of it as a group of specific infectious diseases caused by a variety of pathogenic agents each of which produces an acute febrile illness associated with an inflammatory reaction in the lungs. From the point of view of curative therapy, this concept became important first when type specific antipneumococcus serums were developed, since each serum was useful only against the pneumonia which was caused by the particular type of pneumococcus against which that serum was prepared. The sulfonamides are equally effective against all the pneumococcus types and when these drugs appeared, they essentially replaced specific serums in the treatment of all the pneumococcal pneumonias except in occasional resistant cases. In such cases type specific serums were still helpful.

The sulfonamides have proved effective also in the hemolytic streptococcic pneumonias but even the most effective sulfonamide drugs, namely, sulfathiazole and sulfadiazine, are only moderately effective in staphylococcic pneumonia and even less so in the pneumonias caused by Friedländer's bacillus or by influenza bacillus. Recently, in several parts of the United States there have appeared increasing numbers of cases of hemolytic streptococcic infections, including severe cases of pneumonia, which failed to respond to adequate sulfonamide therapy clinically and which were proved by laboratory tests to be caused by organisms that are resistant to sulfonamides. The situation with respect to the hemolytic streptococcus may be analagous to that which has been universally recognized in gonococcic infections in which the widespread use of sulfonamide therapy has resulted in a steadily increasing proportion of sulfonamide-resistant strains.

Fortunately, penicillin made its appearance in the United States at about the same time. This antibiotic is effective against all types of pneumococci and also against all serological types of group A hemolytic streptococci which include all of the beta hemolytic streptococci that cause pneumonia. In addition, it is the most effective agent available against the pathogenic strains of Staphylococcus aureus and against the alpha hemolytic streptococci which may be responsible for occasional pneumonias. Even penicillin is not effective against the gram-negative bacilli including the Hemophilus influenzae (Pfeiffer's bacillus) and the Klebsiella pneumoniae (Friedländer's bacillus). Streptomycin, which has been used only in very limited clinical and laboratory tests, may prove effective against many of the strains of gram-negative bacilli. None of the known chemotherapeutic or antibiotic agents are effective against the pneumonias

* From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

which are due to virus or rickettsial agents, nor are they effective in the pneumonias of unknown cause which are thought to be of virus etiology.

During the epidemic of influenza A which occurred in 1940 and 1941 an unusually large number of cases of Staphylococcus aureus pneumonia were recognized which occurred mainly as a complication of the influenza. Before that time, the staphylococcus had been recognized as a not infrequent cause of severe pneumonia and laryngotracheobronchitis in infants and young children, and occasionally as the cause of pneumonias complicating other staphylococcic infections (by hematogenous spread). In certain localities, it was the cause of the severe post-influenzal pneumonias during the pandemic of 1918. Since 1941, these staphylococcic pneumonias have been recognized in adults quite frequently in many clinics mostly, but not exclusively, as complications of influenza-like infections. During the 1940 and 1941 outbreak of influenza, it was shown that sulfadiazine and sulfathiazole were effective in varying degrees against these infections. Only in occasional early cases of staphylococcic pneumonia, however, were dramatic results observed in the treatment with these sulfonamides comparable to the responses which regularly follow the use of these same drugs in pneumococcic and streptococcic pneumonias. Penicillin has proved to be far more effective than any other chemotherapeutic or antibiotic now available in the treatment of these staphylococcic infections.

It is thus clear that pneumonia is due to a variety of living agents, bacterial or nonbacterial, and that the best results in each of these kinds of pneumonia will depend upon the choice and proper use of the effective therapeutic agent. What then are the most important etiological agents that cause pneumonia? How can they be recognized and diagnosed? Which effective drugs and anitbiotics are available to combat these specific infections and how are they best used?

*Etiological Agents.* The pathogenic agents which may cause pneumonia include various kinds of bacteria, fungi, rickettsias and viruses. In addition, there have been observed in recent years many cases of pneumonia having the characteristics of virus infections, but in which the etiological agent has not been isolated and proved conclusively. The relative incidence of these different forms of pneumonia varies widely in different countries, in different years and sometimes in different localities in the same country. Some of the salient differential features of the more common among the bacterial pneumonias and of most of the viral pneumonias are given in the accompanying table. The indications for the use of sulfonamides and antibiotics are given in each instance together with the optimum dosage. A few additional comments concerning these pneumonias and some of those not listed may be of interest.

*Pneumococcic Pneumonia.* This form has been declining steadily in frequency in the United States during the last decade except in a few localities. It probably still constitutes the largest proportion of the severe cases of pneumonia throughout the world. It is the easiest to recognize because of the characteristic history, sputum and later the signs of frank consolidation. In these cases, improvement in the acute symptoms, in toxemia and dyspnea often occurs within twelve hours and usually within twenty-four to forty-eight hours after treatment with sulfonamides or penicillin in adequate doses is started. The mortality has been reduced by this treatment from about 30 per cent to less than 10 per cent and the fatalities are limited chiefly to persons over fifty years old, those with severe underlying conditions and patients in whom treatment has been delayed too long.

## DISTINCTIVE FEATURES AND SPECIFIC TREATMENT OF THE COMMON FORMS OF PNEUMONIA

| Clinical and Laboratory Features | Causative Agent | | | | | |
|---|---|---|---|---|---|---|
| | Pneumococcus | Hemolytic Streptococcus | Staphylococcus Aureus | Friedländer's Bacillus | Influenza Bacillus | Viruses (Known or Probable) |
| Occurrence | After common cold or bronchitis | After streptococcic infections (tonsillitis, scarlet fever), measles or influeza | Infancy; early childhood; adults after influenza; or metastatic from other foci | Old persons or those with chronic respiratory infections; alcoholics; complicating urinary or intestinal infections | Infancy; early childhood; adults with chronic bronchopulmonary infections; after influenza virus infections | Predominantly adolescents and young adults. Vary with virus e.g., psittacosis and ornithosis (after exposure to sick birds) |
| History and Symptoms | Sudden onset; shaking chill; localized pleuritic pain | Sudden or gradual; chills or chilly sensations; presternal pain (occasional pleurisy), hoarsness, dyspnea | Sudden or gradual; chills or chilly sensations; dyspnea and presternal pain during or after influenza | Chronic cough; onset with chills, pleurisy and dyspnea; rapid progression | Acute; rapidly progressing; severe prostration, dyspnea, and cyanosis, especially after clinical influenza | Gradual onset, headache, chilly sensations (chill uncommon), dry cough, presternal soreness (pleurisy uncommon) |
| Physical Findings | Suppressed breath sounds and occasional râles early; then lobar consolidation; short grunting respiration | Red throat with exudate; musical and crepitant râles; scattered consolidation; signs of pleural fluid early | Diffuse râles and patchy consolidations; relatively slow pulse in post-influenzal cases | Patchy or confluent bronchopneumonia; very rapid respirations; marked cyanosis; upper lobes frequently involved | Laryngotracheobronchitis in infants; patchy and confluent consolidation | Crackling râles, scattered or migratory; dyspnea and cyanosis on light exertion; patchy atelectasis or consolidation later |
| Sputum | Rust-colored; gram-positive lancet-shaped, encapsulated diplococci prodominant in smears | Blood-streaked or bloody; chains of cocci in smears | Purulent, chalky or mixed with varying amounts of blood (pink to brick red); clumps of cocci in smears | Bloody, mucoid, stringy; numerous stubby gram-negative bacilli with large capsules in smears | Bloody or blood tinged, mucopurulent with fibrin later; short slender pleomorphic gram-negative bacilli in smears | Scant at first; yellowish, mucoid (rarely blood tinged), purulent later, few organisms in smears |
| *X*-ray | Uniform density, lobar distribution | Diffuse patchy densities; pleural fluid early | Peribronchial patchy or nodular densities; confluent with abscesses later | Diffuse patchy densities early; confluent dense consolidation (like fluid) upper lobes frequently involved | Diffuse patchy or miliary densities | Soft nodular (miliary) densities; may spread from hila; areas of consolidation or atelectasis later |
| White Blood Count | 15,000–20,000; mostly polys; (leukopenia in severest cases) | 15,000–30,000; mostly polys with toxic granules | Variable; leukopenia early in post-influenzal cases; elevated later | Leukopenia (2,000–6,000) frequent; toxic polys predominant; elevated later | Leukopenia early | Normal or low; slightly elevated later; increases in monocytes |
| Sulfonamide or Antibiotic Therapy | Sulfadiazine, 4 Gm. then 1 Gm. every 4 hours *or* penicillin 15,000 or 20,000 units every 2 or 3 hours for 24 hours, then 15,000 every 3 hours; stop after 2 or 3 days of normal temperature and subsidence of acute symptoms | Same as for pneumococcus except continue for 5 to 7 days after temperature is normal | Penicillin 20,000 or 25,000 units every 2 or 3 hours depending on severity until temperature reaches normal and acute symptoms subside. Continue 20,000 units every 3 hours for 7 to 14 days longer. Sulfadiazine or sulfathiazole in full doses may be used as a supplement | Sulfadiazine as under pneumococcus; intravenous or subcutaneous injection of 5 Gm. of sodium sulfadiazine may be used for initial dose. Penicillin by inhalation, 50,000 units every 3 or 4 hours may be used. Streptomycin intramuscular or by inhalation when available | Same as for Friedländer's | Sulfonamides and antibiotics not usually effective except when there is complicating bacterial infection as evidenced by purulent sputum with many organisms, leukocytosis, change in clinical course or physical findings, then use in full dose as for bacterial pneumonias |
| Commonest Complication and Its Management | Empyema, usually after first week; thoracentesis and intrapleural injections of penicillin, 50,000 units in 50 to 200 cc. of saline. Repeat at 1 to 3-day intervals so long as purulent or infected fluid forms; surgery after 2 to 3 weeks if indicated | Empyema may develop during first 3 or 4 days; large amounts of serosanguineous, then fibrinopurulent fluid; treatment same as for pneumococcus empyema; surgery only if thick pus or thick-walled cavity persists | Multiple pulmonary abscesses; no additional treatment indicated early; surgery for drainage may be necessary for large abscess which fails to heal. Penicillin by inhalation, 25,000–50,000 units every 3 or 4 hours may be tried first; empyema or pyopneumothorax treat as under pneumococcus | Multiple lung abscesses, may resemble pulmonary tuberculosis with cavitation. Streptomycin by inhalation when available (dosage 20,000–30,000 units every 3 or 4 hours). Recurrence frequent in recovered cases | Obstruction in infants may require intubation or tracheotomy; hemoptysis, pulmonary abscesses or bronchiectasis, especially in post-influenzal cases. Streptomycin by inhalation may prove helpful | Complications infrequent; convalescence may be prolonged with weakness and persistent cough for several weeks |

Purulent complications are infrequent if treatment is undertaken early. Furthermore, empyema, the commonest of these complications, will usually yield to treatment by aspiration of the empyema fluid and instillation of penicillin. If the exudate is very thick, irrigation with saline to remove some of this exudate before instilling the penicillin may help bring about early recovery and avoid open surgical drainage in most cases. Systemic treatment with penicillin or sulfonamides may be continued until the patient remains completely afebrile for several days. The aspirations and the local instillations of penicillin may be discontinued if the fluid remains free of organisms and the patient shows no further signs of active infection, unless it continues to accumulate in appreciable amounts, in which case, the aspirations and penicillin should be continued.

*Streptococcic Pneumonia.* This is a severe and often rapidly advancing form of pneumonia which usually begins with a pharyngitis followed by laryngitis and tracheitis. The mortality in this form of pneumonia is often as high as 40 per cent and young adults are frequently attacked. In many cases, particularly in epidemic forms of the disease which occur during outbreaks of measles, scarlet fever or influenza, there is a rapid accumulation of thin serosanguineous fluid during the first three or four days of the disease while the pulmonary infection is still progressing. This results in a marked increase in dyspnea and toxemia which is often dramatically improved by simple aspiration of the fluid. Nowadays, the administration of sulfonamides and particularly of penicillin may delay or prevent the appearance of this form of empyema and instillation of penicillin into the pleural cavity after aspiration of the fluid may prevent the reappearance of the toxemia and in many instances, bring about a rapid and complete cure without re-accumulation of this fluid. Continued treatment with sulfonamides alone after the fluid becomes thick and purulent may sometimes result in a rigid and thick-walled empyema cavity which may become difficult to obliterate surgically. This can probably be avoided by early evacuation of fluid and penicillin instillations, the latter preceded by saline irrigations if the fluid is thick and fibrinopurulent.

Because of the tendency of this form of pneumonia to be accompanied by abscess formation and other purulent complications, it is best to continue with sulfonamide or penicillin treatment somewhat longer than in cases of pneumococcic pneumonia. Treatment for five to seven days after the temperature has become normal is probably adequate in most cases. The exact mortality in streptococcic pneumonia when properly treated with sulfonamides and penicillin is not known, but it should not be much greater than in the pneumococcic pneumonias.

Most of the streptococcic pneumonias are caused by strains of group A beta hemolytic streptococci and some of these may be resistant to sulfonamide drugs but all are susceptible to penicillin. Occasionally, a similar type of infection is encountered in which the sputum and pleural exudate and sometimes the blood culture yield Streptococcus viridans in pure culture. In such cases, the sulfonamide drugs are of no help and it is necessary to resort entirely to penicillin. The results of penicillin treatment in such cases are usually highly satisfactory.

*Staphylococcic Pneumonia.* This is a form of pneumonia which has always been important in pediatric practice, but it has become increasingly important in adults in recent years. There is a fulminating acute variety which occurs during or after an attack of influenza and which may prove fatal within the first three or four days or even within a few hours of the time when the symptoms or signs of pulmonary involve-

ment are first recognized. Other cases vary all the way from this form to a subacute and chronic fibrosing type of diffuse pneumonia associated with multiple abscess formation and pyothorax. The mortality in staphylococcic pneumonia was usually about 50 per cent and almost all of the fulminating cases proved fatal. With early and adequate sulfonamide and penicillin therapy, some of the patients with apparently fulminating cases have recovered and the mortality and disability among the others has been markedly reduced.

Anatomically, the fulminating type of case is associated with a severe laryngotracheobronchitis and a diffuse hemorrhagic confluent lobular bronchopneumonia. In many areas, usually around the bronchi or bronchioles, there is evidence of necrosis of the alveoli and masses of cocci can be seen in such areas. In the less acute cases, there are numerous peribronchial abscesses which are small at first and later may become confluent and either break into the bronchi or into the pleural cavity. The replacement of some of these abscesses by fibrous tissue results in a chronic type of pneumonia with increasing difficulties in respiration and sometimes death from cor pulmonale. During the first few days of the disease many of the mild or moderately severe cases may be difficult to distinguish by their physical signs and *x*-ray findings and even by their symptoms from cases of primary viral pneumonia. This is particularly true if the white blood cell count is normal or low as is sometimes the case in the early and acute phase of both diseases. The sputum is purulent and often mixed with blood. Smears show many staphylococci which on culture prove to be hemolytic and coagulase positive. The character of the sputum should, therefore, help to differentiate the staphylococcic from the viral pneumonias.

Because of the fact that the staphylococci are much less susceptible to sulfonamides and penicillin than are the pneumococci and streptococci, treatment must be more intensive. If sulfonamide drugs are used, they must be given in larger doses. Usually 8 to 10 Gm. a day are necessary in adults, and it is necessary to give greater amounts of fluid in order to avoid renal complications. When it is possible to obtain blood chemical determination, it is advisable to keep the blood level of sulfadiazine between 10 and 15 mg. per 100 cc. of blood and sulfathiazole between 8 and 10 mg. per 100 cc. (Levels of 7 to 10 mg. per cent of sulfadiazine or 4 to 6 mg. per cent of sulfathiazole are usually adequate in pneumococcic pneumonias.) Since prolonged treatment is indicated, it may be necessary to use these two drugs in succession if drug fever or rash occurs after a week or so of treatment with one of them. The minimum dose of penicillin that should be used in staphylococcal pneumonias is 20,000 units every three hours and larger amounts up to 25,000 units every two hours may be needed early in the severe cases. Furthermore, because of the tendency to form multiple abscesses, the treatment must be prolonged for one to two weeks after the acute symptoms have subsided. This is necessary in order to assure the healing or the evacuation of these abscesses before the antibiotic therapy is stopped. Because of the severe laryngotracheobronchitis that is common in these cases and because the abscesses tend to be peribronchial in location, treatment by inhalation of nebulized penicillin in a manner suggested by Barach may prove helpful and result in more rapid healing. At the present time, it is not possible to say whether sulfonamides are of sufficient additional benefit in penicillin treated patients to warrant the added risks and additional precautions required for their prolonged use in the large doses that are needed.

*Friedländer's Pneumonia.* This is a relatively infrequent, but very severe variety in

which the mortality in acute cases may be as high as 70 to 80 per cent. There are instances of epidemics of this disease recorded in Germany; one in a children's home and the other in a prison camp, and in these outbreaks the mortality was not so high. Intensive sulfadiazine therapy used in the same manner as in severe staphylococcic infections has resulted in reduction in the mortality to about 50 per cent. Occasional cases are reported in which large doses of penicillin have apparently resulted in recovery. Such cases are probably due to strains of Friedländer bacillus which are relatively susceptible to this antibiotic. More recently, streptomycin has been used with considerable success in a very small number of cases in the United States. In this disease, too, there is considerable necrosis of pulmonary tissue resulting probably from ischemia caused by obstruction with the thick gelatinous exudate. Prolonged therapy for one to two weeks after essential recovery is therefore indicated. Inhalation of nebulized antibiotics may prove useful especially after the acute phase when abscess formation begins to take place.

*Pfeiffer Bacillus Pneumonia.* This form was widely prevalent during the pandemic of 1918, and probably before that in 1890. Clinically and pathologically the disease is similar to the fulminating acute forms of hemolytic staphylococcus aureus pneumonia, but less acute forms probably also occur. The mortality in these pneumonias is also quite high. The extreme toxemia and necrosis of tissues that occurs is thought to be due in part at least to the toxic product of the influenza bacillus. The underlying causative agent of pandemic influenza which is presumably a virus, probably also plays an important part in the pathogenesis of these changes. The influenza bacillus may also cause acute laryngotracheobronchitis in infants and young children and occasionally is the cause of pneumonia in adults as a complication of chronic bronchitis or bronchiectasis in which these organisms are frequently found.

The indications for specific treatment are essentially the same as in the Friedländer bacillus infections. The main reliance at present is on intensive sulfonamide therapy with sulfadiazine or sulfathiazole. Occasional strains of influenza bacillus are slightly susceptible to penicillin and when such strains are involved, the use of large parenteral doses of that agent or treatment by inhalation may be effective. Judging from the results in influenza bacillus meningitis, streptomycin may prove to be the most effective agent against these organisms, but there is considerable strain variation in the susceptibility of influenza bacilli to streptomycin. There are as yet no clinical results reported to substantiate the value of streptomycin in influenza bacillus pneumonia.

*Other Bacterial Pneumonias.* There are rare cases of pneumonia due to other cocci such as Micrococcus tetragenous, meningococcus, or Micrococcus catarrhalis and others caused by bacilli such as those of anthrax, plague and tularemia. These pneumonias may be primary or they may be secondary to systemic or other focal infections with the same organisms. The meningococcal infections respond best to sulfonamide therapy while the other coccal and gram-positive bacillary infections should yield to penicillin, alone or combined with sulfonamides. There is evidence that tularemia is highly susceptible to streptomycin and the pneumonic form will probably also respond to this agent. The same may prove to be true of the pneumonic forms of plague.

*Pneumonias Caused by Fungi.* Certain fungus infections, namely, moniliasis and coccidiodomycosis may occur in acute bronchopulmonary forms. Candida albicans is the organism commonly found in bronchopulmonary moniliasis which is said to occur mostly among tea tasters and in persons who

handle grains. The organism, however, is not infrequently found in the mouth of normal individuals and under unusual conditions may give rise to lower respiratory tract infections. It is of interest that the first case of infection with Coccidioides immitis was reported from Argentina, but the total number of authentic cases from South America is very few. The organism is very prevalent among wild rodents in certain parts of western and southwestern United States and most of the human cases of coccidiodomycosis have been recognized in those regions. These bronchopulmonary mycoses are usually subacute or chronic in nature and associated with multiple abscess formation giving a picture which closely simulates pulmonary tuberculosis. Some of the acute forms are not unlike atypical pneumonias of other kinds, particularly early in their course. The characteristic forms of monilia in the sputum are oval, thin-walled, yeast-like cells, 2 to 4 millimicra in size and occasionally mycelial elements and budding forms are found. The sputum usually has a distinct yeasty odor. Coccidioides may appear in sputum as spherical, thin-walled structures, 20 to 80 millimicra in diameter and filled with small round endospores which may eventually be freed by rupture of the cell wall. It is important to recognize these forms of pneumonia early because they are likely to become chronic and then may be confused with pulmonary tuberculosis. There is no effective therapy although iodides are usually used and sometimes seem to be somewhat effective.

*Rickettsial Pneumonias.* A diffuse patchy type of pneumonia has frequently been observed in the course of severe rickettsial infections such as typhus, Rocky Mountain spotted fever and South African tick-bite fever. Although secondary bacterial infections may play a rôle in some of these pneumonias, autopsies in fatal cases have revealed an interstitial type of infiltration in the lungs with mononuclear cells of a type suggestive of rickettsial rather than bacterial infection. Similar pulmonary lesions are easily induced in experimental animals by intranasal infection with rickettsias.

A new form of rickettsial infection called Q fever has been recognized in Australia since 1933. This disease which attacks mostly slaughter house workers and foresters gives a picture like that of severe influenza, but there is an associated "typhoid state" with severe drowsiness and even stupor. The causative agent can be obtained from blood or urine of patients by injection of guinea pigs or mice. After an incubation period of eight to fourteen days, large intracytoplasmic colonies of the rickettsias are seen in impression smears of the spleens of these animals. Specific antibodies to the rickettsias develop in the patients, but agglutinins for proteus X19 or XK do not develop. A similar if not identical rickettsial agent has been found in ticks in the western United States, and sporadic cases of so-called American Q fever have occurred in this region. Laboratory infections, both clinical and latent, have been recognized in Australia and in this country. At least two outbreaks of laboratory infections in this country have been associated with severe atypical pneumonia, which clinically and by *x*-ray were very similar to other atypical pneumonias of unknown etiology, the so-called viral pneumonias. Recently, outbreaks of severe pneumonia due to the same or to a very similar agent have been recognized in the Mediterranean area and cases from this source have apparently been transferred to the United States in military units. No specific treatment is now known for any of these rickettsial infections.

*Pneumonia Caused by Known Viruses.* Certain virus diseases are accompanied in occasional severe cases by pulmonary lesions presumably due to the same agent. Similar

lesions are readily produced in experimental animals by intranasal inoculation of many viruses. Human cases of severe pneumonia due to the virus of lymphocytic choriomeningitis have been described recently and respiratory symptoms have occurred in laboratory workers accidentally infected by inhalation of the virus of lymphogranuloma venereum. Pneumonia complicating measles or smallpox may also be due to these respective viruses although the majority of such pneumonias are probably secondary bacterial infections. Cases of pneumonia apparently acquired from exposure to sick kittens have recently been observed. A virus capable of producing transmissible pulmonary lesions in kittens has also been described, but the relation of this virus to human cases has not been established. The commonest viruses which specifically attack the respiratory tract and produce pneumonia are those of influenza and the psittacosis group of viruses.

*Influenza Virus Pneumonia.* It is well recognized that in many severe cases of clinical influenza there are symptoms, physical signs and *x*-ray findings suggesting involvement of the trachea, bronchi and lungs. Scattered musical and crepitant râles and fine mottled infiltration seen in *x*-ray in the lungs are all that can be made out, but there is usually a severe cough and often bloody sputum. In the extensive pneumonias which occur as a complication of influenza, secondary bacterial infections frequently play a dominant rôle and probably determine the pathological character and the severity of the pulmonary infections in most instances. Some cases, however, have been described in which evidence of bacterial infection could not be demonstrated after careful cultural and histological study of the pulmonary lesions and the pneumonia in those cases most likely is due to infection with influenza virus. An analagous situation is found in experimental influenza virus infections. In certain animals, notably mice and ferrets, the influenza virus alone produces extensive and fatal pulmonary lesions in the absence of bacteria. In swine, however, the influenza virus alone produces only a mild infection with involvement limited to the upper respiratory tract simulating ordinary cases of human clinical influenza. A combination of the virus with influenza bacillus produces an extensive pneumonia which is highly fatal to swine but the bacillus itself does not produce pulmonary lesions in the absence of a virus. The situation in the swine may, therefore, be analagous to that found in the severe pneumonias observed in the pandemic of 1918 in which influenza bacillus was found in pure culture. The recent demonstration of a soluble toxin in influenza A virus may help to explain some of the severe hemorrhagic lesions which result in uncomplicated virus infection.

There is no known specific treatment of influenza virus infections. Cases in which secondary bacterial infection is present should be treated vigorously for that particular bacterial infection. The evidence that beneficial effects can be obtained from influenza antiserums or from convalescent serums is inconclusive. Favorable results have been obtained recently in the prevention of infections with the viruses of influenza A and B by inoculation of vaccine containing these viruses. The vaccine must be given from ten days to a few months in advance of exposure.

*Psittacosis, Ornithosis and Related Infections.* Psittacosis has been recognized since 1880 as a severe disease acquired from sick parrots and clinically resembles influenza on the one hand, and typhoid on the other. The chief pathological finding is an atypical pneumonia. The virus etiology of this disease was established during the pandemic of 1929 and 1930 which arose from an epizootic among Brazilian parrots and was first re-

ported from Buenos Aires. The causative agent has been found in many species of exotic birds and related viruses are widespread among pigeons and many other species of wild and domestic fowl. Infections acquired from the latter viruses are called "ornithosis" as suggested by Meyer. Other serologically related filtrable viruses are found in normal laboratory animals and are capable of producing pulmonary lesions in those animals, and these serve to confuse the results of inoculations with human materials. In addition, still other viruses which are responsible for such entirely different diseases as lymphogranuloma venereum, inclusion conjunctivitis and trachoma are immunologically closely related to the viruses of psittacosis and ornithosis and offer another source of confusion in serological tests.

Clinically, the only features which distinguish psittacosis and ornithosis from other primary non-bacterial pneumonias is the severity of the course and the "typhoid picture." The diagnosis is suspected by the history of exposure to sick birds and may be established by inoculation of sputum or material aspirated from the lungs into mice or guinea pigs and then demonstrating the characteristic coccobacillary inclusions in impression smears of the spleen. The different species of viruses vary in their pathogenicity for different animals and in the susceptibility of animals to inoculation by different routes.

Because of the widespread occurrence of these viruses among many common varieties of birds, ornithosis was thought to be the cause of the widely prevalent cases of so-called virus pneumonia. Extensive attempts to obtain these viruses in such cases and to prove their etiological relationship by serological studies have not borne out this suspicion. The proved human cases have been limited almost entirely to persons intimately exposed to sick birds. A small outbreak of severe pneumonitis with a high mortality has recently been described in Louisiana and a new virus of this same group was proved to be the causative agent in these cases. Still another related virus was isolated from two fatal cases in Illinois.

Although the viruses of lymphogranuloma venereum, inclusion conjunctivitis and trachoma are susceptible to sulfonamides, these drugs have little or no effect on psittacosis or ornithosis. Occasional strains may prove to be susceptible to penicillin or to other antibiotics especially if they are given early and in comparatively large doses. Secondary bacterial infections are not uncommon in these cases and may greatly increase the severity of these pneumonias. In that event, the appropriate antibacterial agent given in full doses may bring about considerable improvement.

*Primary Pneumonia of Unknown Etiology—"Virus Pneumonia."* This form of pneumonia has been recognized during the past few years in military establishments, schools, colleges and among hospital personnel, especially doctors, nurses and attendants. It is now being recognized with increasing frequency in general civilian and hospital practice, although the diagnosis is undoubtedly being made much more often than is warranted. The cases have been variously referred to as "influenza pneumonia," atypical bronchopneumonia, disseminated focal pneumonia, acute pneumonitis, and by many other designations. The official terminology adopted for classification purposes by the United States Army was "primary atypical pneumonia, etiology unknown," but the disease is generally referred to by the name originally suggested by Reimann, namely, "virus pneumonia." The same writer has more recently suggested the term "viroid." Outbreaks of this disease have been described in isolated camps, schools and institutions prior to 1940, but it assumed epidemic proportions in the United

States and Great Britain during 1942 and 1943.

The clinical features of this disease are quite similar to those of other pneumonias caused by known viruses or rickettsias and are listed in the table. In this disease, however, there are widespread variations in the severity of the symptoms and in the extent of the pulmonary lesion. The majority of cases in adolescents and young adults are mild and may involve only a portion of one or both lungs extending out slightly from the hilum. Others involve most or all of both lungs and may give a picture which on physical examination and by *x*-ray closely resembles that of acute miliary tuberculosis. Cases of the latter type may be extremely severe and may have marked dyspnea and cyanosis. Headache may be a prominent feature in the majority of cases, even the mild ones. Cough is often very irritating and unproductive for several days. Both of these symptoms may be difficult to control with the usual remedies. The fever may be irregular or sustained but usually is not higher than 103°F. It may continue for anywhere from three to twenty-one days or even longer, but in the majority of cases the febrile course lasts from seven to fourteen days. Pleurisy and complications other than prolonged cough and asthenia are uncommon.

The blood in many cases, especially the severe ones, may develop cold agglutinins; that is, the serum or plasma develops the property of agglutinating human red blood cells irrespective of the blood group and including the patients own cells when exposed to the cold. These cold agglutinins first appear during the middle of the second week of the disease, reach a maximum titer within a few days and may then decline or disappear quite rapidly. If the titer of cold agglutinins in the blood is very high, agglutination of the red blood cells may take place at room temperature and may be recognized by the difficulty in making blood counts due to the clumping of the red blood cells. Significant titers of cold agglutinins rarely develop in the course of other acute respiratory infections or in other virus diseases and may, therefore, serve as an aid in the differential diagnosis. Workers at the Rockefeller Institute have isolated a capsulated strain of indifferent streptococcus and demonstrated the development of agglutinins for this streptococcus in convalescent serums from these cases.

Many attempts have been made to isolate the causative virus from cases of this sort. As already intimated, known viruses or rickettsial agents including those of psittacosis, ornithosis and Q fever account for a neglible proportion of these cases. That a filtrable agent is the cause, at least of some characteristic cases of this disease, has been demonstrated by a carefully controlled experiment in humans carried out by the Commission on Acute Respiratory Diseases of the United States Army. Human volunteers inhaled filtered sputum from typical cases and developed identical clinical symptoms and physical and *x*-ray signs as were found in the cases from which the sputum was obtained. Boiled sputum failed to reproduce the disease. A rise in cold agglutinins occurred in the experimentally induced cases. Many attempts by the same workers to transmit the disease to experimental animals by similar material from comparable cases have failed. Several other groups of workers, however, have isolated filtrable agents and produced lesions in animals with materials from human cases. Eaton and his co-workers in California isolated a virus which they were able to propagate in fertile hen's eggs and which was neutralized by the convalescent serum of a number of characteristic cases of this disease, but not by the serums of cases from other diseases. None

of these findings have been adequately confirmed.

There is no specific treatment in this form of pneumonia. Sulfonamide drugs and penicillin are indicated when there is any reason to suspect secondary bacterial invasion by the change in the character of fever, the occurrence of leukocytosis or purulent sputum and particularly by the demonstration of bacteria in large numbers in the sputum.

When used, these agents should be given in full doses as indicated by the type of predominant organism seen in the smears or obtained in cultures. The mortality in these cases is low, but there may be a long period of asthenia with persistent cough after the febrile course in many cases.

# Curare*

## *A Review of Its Therapeutic Effects and Their Physiological Basis*

EDWARD B. SCHLESINGER, M.D.†

NEW YORK, NEW YORK

THE clinical use of curare is based on its ability to create a transient block to neuromuscular transmission. This phenomenon was first described by Claude Bernard,[1] who demonstrated that the site of action of the drug was at some point between the nerve fiber and the muscle.

*Historical Background.* It was tribal custom in widespread areas of South America to prepare arrow poisons from plants indigenous to the local region. Collectively these crude extracts were known as curare. As prepared, they contained various alkaloid fractions in differing proportions. These alkaloids often had many pharmacologic effects other than those described by Bernard in his experiments. The samples reaching civilization naturally varied widely in origin and alkaloid content.[2]

Since the source of supply was so equivocal and the active agent poorly understood, curare until recently remained an unpredictable therapeutic tool. Nevertheless, it is surprising with what speed the properties of the drug were exploited. Jousset,[3] Benedikt[4] and others used curare clinically almost as soon as Bernard's experiments were complete. Due to the lack of a reliable preparation rather than to a paucity of interest, clinical experimentation remained dormant for many years. The literature of the period, however, is of intense historical interest.

In recent years, important steps were taken by King,[5] and by Wintersteiner and Dutcher,[6] in isolating and identifying a pure crystalline tubocurarine from the vast number of specimens available. Knowledge of the alkaloid previously was confused both as to its exact botanical origin and pharmacologic properties. With this clarification, it was possible to investigate a drug of predictable properties and toxicity. The determination of its exact mode of action at the myoneural junction, however, is still incompletely realized.

Tubocurarine is now known to be a quaternary ammonium salt. Such salts, in general, have the property of paralyzing conduction at the myoneural junction.[7] Among the group, however, tubocurarine is the only alkaloid which, in certain definite concentrations, has an almost pure myoneural junction effect. This property, of great clinical significance, is most probably related to the configuration of the molecule as well as to chemical composition. Acetyl choline and prostigmin have a similar configuration and under certain circumstances can be made to cause or degrees a muscle twitch.[8] Molecules of this stereochemic type exert specific effects on vital membrane structure. Further study of these membrane phenomena will add to our knowledge of the physiological action of quaternary ammonium salts and the mechanism of neuromuscular conduction.

Recent physiological data[9,10,11,12,13] make

* From the Department of Neurology, College of Physicians and Surgeons, Columbia University, and the Neurological Institute of New York.

† Teagle Fellow in Research Neurology.

the following hypothesis a probable one. The myoneural junction is an excitable membrane. A transmitter substance, whether it be acetyl choline or local action currents, induces a potential by actively depolarizing the junctional region. Normally, this depolarization reaches a critical value and produces the muscle spike by spreading electrotonically and depolarizing the neighboring area. In fully curarized muscle, this so-called end plate potential rises to a subthreshold level and then decays without initiating a muscle response. If curare merely paralyzed skeletal muscle in this manner, it would have limited clinical value other than in therapy requiring a paralyzant effect. Actually, the size of the end plate potential depends, to some extent, on the concentration of drug. Therefore, the degree of block can be controlled. Frequencies outside a critical range, or abnormally sustained, can be blocked while those of different characteristics will still evoke a normal muscle twitch. Since the normal excitatory state at the junctional membrane depends on rapid reversibility of polarization, any mechanism which either reduces this capacity or maintains the membrane in a single phase for abnormal periods of time acts as a depressant. Such a process may explain why in certain concentrations acetyl choline and prostigmin are depressants of neuromuscular conduction.

These observations underlie the present-day concept of curare therapy. We do not always attempt to paralyze the myoneural junction, but sometimes desire to create a block to certain frequencies imposed on the myoneural junction by the disease process. It is thus perfectly feasible to obtain a therapeutic effect without los of voluntary power.

## CLINICAL APPLICATIONS

From the foregoing, it becomes obvious that the clinical use of curare depends upon maintaining varying degrees of block to neuromuscular conduction. On this basis a sharp division may be made amongst its various applications:

I. *Where total or subtotal block is necessary* (paralyzant effect)
   - A. Surgical anesthesia
   - B. Shock therapy
   - C. Amelioration of convulsions, as in tetanus

II. *Where partial block is desired* (lissive effect)
   - A. Muscle spasm
     1. As in actual trauma to muscle, myositis
     2. Reflex spasm, in orthopedic disturbances, low back syndrome, etc.
     3. With arthritis, acute
   - B. Spasticity
     1. Spinal cord injury
     2. Birth injury
     3. Degenerative diseases of the CNS
   - C. Rigidity
     1. Paralysis agitans
   - D. Dystonia and athetosis
   - E. States resembling spasm and spasticity as in poliomyelitis

### IA. USE OF CURARE IN SURGICAL ANESTHESIA

In 1930, Dr. de Caux,* in England, experimented unsuccessfully with the use of curare combined with nitrous oxide in surgical anesthesia. His failure was undoubtedly due to the crude preparation then available. Griffith,[14] of Montreal, in 1942, published for the first time a description of the clinical use of curare as an adjuvant to anesthesia. His original work was done at the suggestion of Dr. L. A. Wright of New York. Many papers have since defined the useful technics, among them admirable contributions from the original observers.

The preparation in use today is an aque-

* Personal communication.

ous solution containing 20 mg. or units of standard curare per cc. It is titrated for potency by the head drop test in rabbits, which gives an excellent end point. It is apparently a stable and predictable agent.

Clinical experimentation has brought out the need for adequate premedication.[15] Drugs of the hyoscyamus series are useful in preventing excessive salivation and mucus. It should be borne in mind that the dangers of aspiration are heightened by curare, which depresses the pharyngeal reflexes.[16] Intubation is indicated whenever aspiration or regurgitation is a problem.

*Choice of Anesthetic.* Every anesthetic has well defined properties which govern its occasional choice. The ability of curare to add specific degrees of muscle relaxation[17] to all forms of anesthesia has increased the usefulness of some agents which would otherwise be severely limited in value. In addition, the anesthesia concentration need not be carried to the levels previously necessary, since relaxation can be effectively maintained without classical third-stage anesthesia. With good relaxation, trauma can be reduced and operating time cut down. Postoperative complications incident to prolonged anesthesia can likewise be reduced. Consciousness and normal reflexes can be returned much more rapidly because of the low concentrations of anesthetic needed.

A large body of evidence has been collected with regard to the usefulness of curare in combination with various anesthetic agents:

Cyclopropane[18] has proven particularly good in combination with curare. The patient can be kept at a light level of anesthesia and the cardiac irregularities associated with high concentrations of cyclopropane avoided.

Ether: This drug is in itself capable of a curariform effect in clinical concentrations.[19] The dosage of curare must, therefore, be significantly lessened to avoid overdosage. With lowered concentrations of ether, the nausea, vomiting and acidosis of the post-ether recovery period can be markedly lessened.

Sodium Pentothal: Use of pentothal with curare combines two respiratory depressants. However, with adequate control of respiratory exchange the risk is not great.[20,21,22] The quantity of pentothal can be sharply cut down, and its poor relaxant qualities circumvented while its admirable qualities such as ease of administration can be fully utilized.

Ethylene and Nitrous Oxide:[21,22,23] The special properties of these agents can be much more fully exploited when predictable relaxation is added.

Spinal Anesthesia: The results with curare compare favorably with those obtained in spinal anesthesia.[19] Intrathecal therapy is avoided, and the unpleasant nausea and pulling sensation during spinal anesthesia eliminated. High abdominal surgery can be performed with general anesthetics with facility equal to the best results obtained under spinal anesthesia.

*Method of Administration.* The aqueous preparation contains 20 units of standard curare to the cc. Intravenous injection is used except rarely when intramuscular administration is employed. The latter is associated with a slower onset of desired effect and a more prolonged period of relaxation.

Dosage requirements vary. Among the factors involved are body weight, anesthetic agent, area of incision and type of disorder. The average dose is 5 cc. or 100 units, given over a period of ten seconds. The dosage is calculated from the foregoing criteria, and the individual experience and preference of the anesthetist. A clinical response is noted within two minutes if the drug is given intravenously and within fifteen minutes when given intramuscularly. Opinion is

divided as to the exact technic of administration. In certain clinics a large single initial dose is given. Elsewhere, divided injections are used, with drug added as indicated by the needs of the surgeon. Large doses given very rapidly may cause respiratory paralysis with a fall in blood pressure incident to the pooling of blood in the extremities. Where normal alveolar exchange is not rapidly facilitated, $CO_2$ may collect with a secondary abrupt rise in blood pressure.[24] This state responds rapidly to normal respiratory exchange.

Because of the rapid effect, the drug is usually injected a few moments before the peritoneum is opened. With average doses, the period of relaxation lasts approximately twenty-five minutes. During this period the surgeon has the advantage of good relaxation, even though the patient may be carried at unusually light levels of anesthesia.

When, for pertinent reasons or not, complete respiratory paralysis occurs, use of positive pressure to facilitate respiratory exchange will, if properly maintained, result in return of adequate spontaneous excursion within five minutes or less. Prostigmin may hasten this return, but is usually unnecessary. An adequate airway and good exchange are the best antidotes. It should be emphasized that the indication for curare therapy is the induction of motor relaxation during surgical procedures. Its use to lessen difficulties incident to poor induction or poor choice of anesthesia is to be decried.

*Endoscopy.* The technics of the use of curare to facilitate laryngoscopy, esophagoscopy and bronchoscopy are well documented and fully substantiated.[25] Bronchospasm as a complication of curare therapy has been reported and deserves further study.[26] However, experience seems to be that care in the rate of administration and choice of dosage will help to avoid this complication.

In summary, it can be stated that the anesthetist has for the first time a tool easy of handling, rarely toxic, capable of affording predictable relaxation during surgery. The opportunity to carry patients at light levels of anesthesia has contributed greatly to a reduction in operative and postoperative complication. Curare seems to be a permanent addition to the battery of anesthetic aids.

## CLINICAL OBSERVATIONS DURING CURARIZATION

Curarization progresses in orderly fashion under normal circumstances. The small striated muscles are first affected. These include the stapedius and tensor tympani, the extra-ocular muscles of the eye and the small muscles of the toes. As the concentration rises, the last muscle to be involved is the diaphragm. Fortunately, from a clinical standpoint, relaxation of the abdominal muscles occurs well before the diaphragm is affected.

The patient first notes a fuzziness of vision, probably related to iris relaxation. Coincidence or careful testing will reveal increased aural sensitivity to low notes, based on a loss of the protective action of the tensor tympani and stapedius. A feeling of warmth and flushing in the extremities may be described. Double vision next appears. Many patients describe a headache in the frontal region, most often a circumscribed area on the left. Dizziness may be noted. Whether this subjective sensation is central or related to the visual changes and a slight drop in systolic pressure is not known.

These phenomena are followed by a feeling of pleasurable relaxation as the larger skeletal muscles are affected. At this point a drop of about 20 points in systolic pressure is recorded. Drowsiness may now supervene. About 10 per cent of patients consistently describe a feeling of euphoria

or "jag" during this stage. In others, a slightly higher level is accompanied by a feeling of tension and increased muscle awareness. As the concentration increases relaxation merges into paresis and paralysis of striated muscle. There is no true hypnotic or sedative effect but if the blood level is rapidly pushed further an abrupt loss of consciousness may occur, unrelated to adequate respiration.

All these effects rapidly disappear as curare is eliminated by the renal apparatus. Intramuscular administration results in a less abrupt onset and a more prolonged duration of curarization. With subcutaneous injection, absorption is irregular, unpredictable, but generally slower. No residual effects on the general body economy have been reported. However, an apparently cumulative or less transient effect on the myoneural apparatus is consistently observed. Since no adequate method of titration of blood levels is available, the basis of this clinical observation cannot be determined.

Ruskin and his associates[27] studied the electrocardiograms of curarized patients and found no change suggestive of a curare effect in therapeutic doses. Other reports in experimental animals and man corroborate this lack of a significant cardiovascular effect of pure tubocurarine. When curarization reaches levels beyond myoneural effects, there may be changes associated with involvement of the autonomic nervous system, or with the asphyxia of respiratory paralysis. Therapeutic applications require levels well below that required for the aforementioned effects.

### IB. SHOCK THERAPY

In 1940, Bennett,[28] of Omaha, aware of the vast therapeutic opportunities inherent in the properties of curare, suggested its use in shock therapy and collected a series of cases in which curare was used for the prevention of skeletal injury during shock therapy. His material was admirably presented and his technics are relatively unchanged to date. Curare unquestionably softens the convulsion incident to shock therapy,[29,30] and thus aids the prevention of some of the common complications, such as crush fracture, etc.

*Mode of Administration.* An intravenous injection of an aqueous solution of curare is started two minutes before the shocking agent is applied. One mg. of curare seems to curarize effectively 2 pounds of body weight. The speed of injection influences the rate and degree of curarization.[31]

Although this form of therapy is widely used, it has not gained the universal acceptance given curare by the anesthesiologists. The explanation may well lie in the fact that the cases are very often handled under conditions far different from the operating theatre. Patients are treated most often in their own beds and given doses of curare that anesthetists might use with impunity. Premedication with atropine or scopolamine is rare and the period of observation frequently short. Indeed, one is struck by how few accidents have been reported in the literature.

Under the conditions outlined by the original workers,[28,32] however, curare has been useful in the prevention of injury and in the protection of patients in whom shock therapy might otherwise be contraindicated.

Electroencephalograms obtained in patients before and during treatment have shown no variation which might be assigned to curarization,[33] except in the occasional dropping out of scalp muscle artefact. However, at certain levels during prolonged curarization a marked drop in brain wave potential has been observed. It is of interest that one observer has reported that, in spite of controlled respiration, there was consistent loss of consciousness in all patients

given critically large doses of intravenous curare preliminary to surgery.[16]

### IC. TETANUS

Although tetanus in most western countries is a relatively minor problem, in the Middle East it is a formidable one. Extensive use of antitoxin alone does not prevent a high mortality. The period of abnormal motor activity or convulsion is poorly controlled by conventional medication and at great cost to body economy.

The use of curare in the amelioration of these convulsions requires great skill and constant observation. Prolonged curarization can result in a state similar to surgical shock.[34] Devoid of the pumping action of normally innervated muscles, the limbs act as reservoirs, with circulating blood reduced and shock eventually supervening. The prevention of this syndrome requires several prophylactic maneuvers. Before curare is administered, the patient must be carefully bandaged to prevent vascular pooling in the extremities. Likewise a snug scultetus binder should be applied to prevent splanchnic pooling incident to relaxation of the abdominal muscles. During treatment, blood volume must be followed closely and fluid intake and plasma volume controlled.

Curare therapy has proven of great value in tetanus. West,[35] Cullen,[36] among others, have contributed to the literature which contains many excellent studies.[37,38,39,40,41,42,43,44] Others have documented the dangers inherent in the technic.[34] One line of approach takes advantage of the availability of aqueous (rapid-acting), and oil suspended (slow-acting) preparations.* The patient is curarized fairly rapidly with aqueous curare and the oil suspension added until an adequate base level is achieved. This level can then be supplemented by additional aqueous curare when necessary. The combination may be utilized in very much the same manner as are protamine zinc insulin and standard insulin.

* *D*-tubocurarine chloride in oil and wax has been used, according to this technic, in five consecutive, cases of severe tetanus with successful outcome.

### II. USE OF CURARE TO OBTAIN A LISSIVE OR RELAXANT EFFECT WITHOUT LOSS OF VOLUNTARY STRENGTH

The experiments of Bremer and Titeca,[45] in 1927, and Hartridge and West,[46] in 1931, greatly extended our understanding of the nature of action and the clinical value of the drug. Bremer demonstrated that small, non-paralyzing concentrations had a specific effect on muscle "tonus." West, in 1931, described a lissive or relaxant action, accompanied by little or no loss of voluntary power. His clinical investigations included the use of curare in reducing spasticity and rigidity. This important work was badly hampered by the lack of a reliable preparation. He was fully aware of the variability of specimens and of the vast number of alkaloids of the same generic type but of differing effect. His investigations remain the groundwork of present day curare therapy of this type.

The availability of a preparation of standard properties in recent years has given great impetus to both physiological and clinical investigation. The aqueous solution has proven very efficient in the induction of neuromuscular block, as described previously. As a means of creating a transient partial block it has been much less satisfactory. Its usefulness has been sharply limited by its narrow therapeutic margin and evanescent effect, in spite of a sound physiological basis.

West,[2] Burman,[47] Bennett[48] and others have described the use of aqueous preparations in syndromes exhibiting spasticity, rigidity and involuntary movement. They noted demonstrable clinical reduction in abnormal activity. This effect, however, was usually exceedingly transient and therefore of questionable therapeutic value. In

cases of cerebral palsy, Denhoff and Bradley[49] found that the initial period of response to effective doses was characterized by masked facies, head drop and mental confusion. After these effects wore off, the useful clinical effect became evident.

These clinical investigations were carried out with aqueous solutions, administered intravenously or intramuscularly. Practically all observers have been unanimous in their dissatisfaction with the evanescent clinical response and the concomitant side reactions. Absorption is followed by high blood levels and rapid elimination: At those high levels, central and peripheral effects occur together. Along with relaxation, the classical signs of curarization supervene. These include dizziness, blurred vision, diplopia, head drop, asthenia and mental confusion. Prolongation of the desired effect at designated levels is difficult or impossible to achieve.

*Long-Acting Preparations.* In an attempt to prolong the desired action and avoid the unpleasant side-effects incident to uncontrolled concentrations, various measures have been tried. An oil and wax suspension, similar to that devised by Romansky[50] for penicillin, was prepared by Schlesinger[51] in 1945 and first reported in a series of cases with spasticity following injury to the spinal cord. A series of 200 cases has since been reported by the same author.[52]

This preparation consists of a suspension of 3 per cent *d*-tubocurarine chloride in 4.8 per cent white wax and peanut oil. It yields a slow-acting curare effect, lasting in some instances more than three days. With dosages which afford good clinical response in certain syndromes, no unpleasant curare side-effects are seen. Occasionally, during adjustment of dosage levels, blurring of vision, diplopia or dizziness has been noted.

In therapeutic dosage range, the drug has been singularly free of side-effects and has shown no tendency to disturb normal body economy or cause habituation. Statistically, spasm, spasticity and rigidity are affected in order of decreasing efficiency. Dosage levels are complicated, and more strikingly related to the degree of motor acceleration than to body weight. Duration of clinical effect likewise seems inversely proportionate to the degree of motor abnormal activity.

Where partial block of neuromuscular conduction is desired, the usefulness of a long-acting preparation becomes apparent. In the syndromes to be described below, the availability of *d*-tubocurarine in oil and wax answers the previous objections to curare therapy. The patients in this series have largely been ambulatory and at their usual vocation.

### IIA. MUSCLE SPASM

The term "muscle spasm" is widely and loosely used but very difficult to define. It may be considered as a state of transient contraction, not amenable to voluntary control, characterized by increased shortening reaction and usually associated with pain on attempted extension.

Clinically, the syndrome is well recognized. It may be a reaction to muscle irritation, inflammatory or traumatic. Frequently, it is reflex in origin and secondary to visceral disorders of like segmental nervous connections. Kellgren,[53] Wolff[54] and others have shown that reflex spasm may be perpetuated after cessation of the initiating stimuli. Such a picture is well represented by the vicious cycle of pain and spasm in low back injury. The initiating trauma is followed by muscle splinting, then pain, then further muscle splinting. Dramatic relief may be afforded by any agent which seems temporarily to break up the cycle. Heat, novocaine injections, etc., have at times served this purpose in individual cases.

Since curare is a physiological muscle relaxant, it is not surprising that muscle spasm responds so well. It has been consistently possible to break up true muscle spasm when the initiating condition is static or brought under control. Where the local pain and spasm are secondary to root compression, radicular pain persists after reduction of the reflex spasm. This response may be a useful clinical test.

### IIB. SPASTICITY

Spasticity is characterized by increased excitability of the stretch reflex. Motion, passive or active, is accompanied by reactive muscle contraction which interferes with useful motor function. An attempt is made to saturate the patient with curare at blood levels which do not interfere with voluntary function but reduce stretch reflex sensitivity. This unmasking of voluntary power, if present, results in increased motor efficiency. Retraining is then imperative in order to rebuild muscle volume and useful habit patterns.

In *spastic paraplegia*, the use of curare in oil has proved a valuable adjunct to treatment. These cases have always been most difficult to handle, and no adequate measure has yet been described which will alleviate the distressing reflex manifestations of this condition with complete success.

In these cases it has been possible to: (1) reduce mass movements and thus aid healing of decubiti and prevent sudden expulsion of urine; (2) prevent contractures, and (3) permit active physiotherapy without acceleration of reflex spasm.

In *spastic paraparesis*, it is sometimes possible to relieve crippling spasticity without resort to surgery. Such surgical procedures take a toll in reduced motor power. Early rehabilitation of the patient is necessary to prevent deformity and atrophy. With good reduction in stretch excitability, the physiotherapist can work to this end. Without such reduction, physiotherapy merely acts as a stimulant to reflex activity.

In spasticity, the duration of effect is of better than average duration and, in general, patients do not return to their original level of dysfunction if therapy is stopped.

*Birth Injuries, Cerebral Diplegia or Spasticity with Dystonic Features.* In his monograph on disorders of the central nervous system in children, Crothers[55] states: " . . . it is essential to develop every motor asset in sight. This conservation and development of assets is procured by two different but closely coordinated methods: First and always, by training, and second by procedures which avoid or correct contractures." Achievement of both these objectives is facilitated by the use of curare in oil. Training capacity is markedly enhanced by the reduction of abnormal activity, with a consequent increase in motor efficiency. The same reduction in spasticity or abnormal muscle tensions also allows a range of motion and activity which prevents further fixation deformity or contracture. Unlike surgical procedures designed to this end, it is unnecessary to destroy innervation or reduce the number of functioning motor elements contributing to the deformity. Effective diminution in abnormal motor activity can be obtained without perceptible loss of motor power.

One has only to watch these children at school to realize the titanic effort which goes into every attempt at motor performance. In light of this, the degree of their achievement under this form of therapy might seem slight to the casual observer. Nevertheless, by objective performance standards the improvement in motor performance is striking. The same tremendous drive which characterizes their usual effort now pushes their performance levels forward at rapid rates.

Improvement may be expected in the following sequence: (1) speech, (2) ability to sit quietly, (3) gait, (4) eating, writing, and performance of skilled motor activities. These patients have maintained their improvement on doses twice weekly.

### IIC. RIGIDITY, AS IN PARALYSIS AGITANS

Evaluation of treatment in these cases is most difficult. It can be definitely stated that rigidity is an indication, tremor is not. Rigidity associated with extreme discomfort, immobility and beginning contracture can be partially alleviated. Sleep is usually improved. Pain associated with long standing muscle tension can be influenced to a gratifying degree. In rigidity there is, however, a wide disparity in response and in dosage tolerated.

It is not surprising that there should be such a wide variance between the effects in spasticity and in rigidity. Spasticity depends upon hyperexcitability of reflex mechanisms such as the stretch reflex, whereas rigidity is a function of simultaneous innervation of agonists and antagonists in addition to reflex mechanisms.

### IID. DYSTONIA AND ATHETOSIS

It has been possible to: (1) reduce spontaneous movements so that patients can sit quietly for reasonable periods, (2) make active exercise and motor training possible, often for the first time, (3) improve sleep.

*General Observations.* Patients almost invariably note a pleasurable feeling of relaxation within two hours after injection. Under favorable conditions, in fact, most of them doze during this period. There is an associated fall in systolic pressure, averaging 20 mg. Hg, which is related to muscle relaxation and is not a specific vascular effect.

Recognizing the general sedative effect, a series of cases showing motor acceleration on a psychiatric basis has been treated. The early results are inconclusive at this time.

No toxic or side-effects of clinical significance have occurred in the therapeutic range. Once concentrations pass a critical level, however, central effects supervene, with mental confusion and a feeling of marked tenseness in addition to the classical toxic signs.

There have been no toxic effects on any organ system over long periods of time and no changes in body economy or general well being. No tendency to habituation has appeared in this series, although one patient has had more than seventy-five injections. Contraindications specifically are: (1) any myasthenic tendency and (2) kidney disease. Since curare is eliminated largely unchanged in the urine, poor renal function conceivably could elevate blood concentrations to a dangerous degree.

### TUBOCURARINE IN OIL AND WAX

*Method of Administration and Dosage Requirements.* Crystalline *d*-tubocurarine chloride is suspended in peanut or sesame oil and white wax. The preparation in use today contains the equivalent of 175 units of standard curare per cc. The preparation is stable and can be sterilized repeatedly. The average dose is 1 cc. $\pm$ 0.25.

Intramuscular injection in the gluteus is most frequently used, although when a patient is well saturated, the subcutaneous route may be used for its slower absorption curve. Dosage is determined by clinical observation, the most efficient below loss of voluntary motor power being chosen. Duration of effect is likewise gauged clinically, the greater number of patients requiring injections every seventy-two hours.

Where possible, electromyography is utilized to check the change in stretch reflex as an objective index of effectiveness of dosage levels.

*Technical precautions* are: (1) prevention of dilution by fluid in syringe or needle, (2) choice of site of injection away from

vascular channels, (3) vigorous shaking to prevent dropping out of suspension, and (4) avoidance of massage of area of injection.

### IIF. USE OF CURARE IN STATES RESEMBLING SPASM AND SPASTICITY AS IN POLIOMYELITIS

The treatment of acute and subacute anterior poliomyelitis consists largely in the alleviation of symptoms and the prevention of deformity and loss of motor function. The fact that there is no specific therapy perhaps throws undue emphasis on forms of symptomatic relief.

During the early phases of the disease or acute febrile illness, meningeal inflammatory reaction occurs, accompanied by root irritation. This is followed by what appears to be muscle spasm. Certainly root irritation is capable of initiating hyperesthesia and reflex muscle spasm. In addition, there may be actual inflammatory reaction in the muscles per se characterized by muscle shortening, resistance to stretch, pain and tenderness. A similar picture is seen in acute rheumatoid arthritis. Spasticity also can be elicited at times and seems to be present when the muscles are studied electromyographically. The exact definition and mechanism of these states resembling spasm and spasticity is not completely clear. Bodian recently has demonstrated spasticity in the experimental animal following intracerebral inoculation of virus. Such studies may afford a much needed clarification of the underlying pathological processes.

The similarity of the clinical picture to true muscle spasm and spasticity makes a trial of curare a rational procedure. Ransohoff,[56] and subsequently Fox[57] have reported a series of such trials. The former reports marked reduction in pain, relief of muscle spasm, and earlier capacity for exercise following the use of curare in aqueous solution. Dosage requirements are obviously complicated by variations in the clinical picture but the basic schedule used is 0.9 unit per kilo of body weight. Fox finds curare a dangerous tool and one difficult to evaluate. Obviously further investigation is required. The usefulness of slower-acting, and probably more easily controlled, oily suspensions of the drug is undergoing detailed study.

Ransohoff adds to the description of the use of curare a therapeutic code of his own, namely, active motion in spite of severe pain. One must be careful to judge this refinement of therapy on its own merit rather than to consider it an integral part of curare therapy in poliomyelitis.

### PROSTIGMIN AS A DEPRESSANT OF NEUROMUSCULAR CONDUCTION

The fact that prostigmin and curare are, at least in part, pharmacological antagonists makes the recent literature on prostigmin of special interest. Since 1940[58,59,60] there have been successive reports on the use of prostigmin, or physostigmine and atropine in a variety of conditions including muscle spasm, spasticity, contracture, muscular pain, weakness, incoordination and fatigue in chronic rheumatoid arthritis, following fractures and other injuries, hemiplegia, spastic cerebral palsy, subacromial bursitis, facial paralysis, stiff neck and low back pain.

The description of a beneficial effect of prostigmin as a depressant of neuromuscular activity at first appears paradoxical to one familiar with the conventional pharmacological concepts of prostigmin effects. Kabat, and his associates, however, have prefaced their clinical presentations with an interesting hypothesis as to its mode of action. The experiments of Schweitzer and Wright[61,62] in 1937 form the basis of the theory. These investigators found that the usual effects of prostigmin did not occur under certain laboratory conditions. If, in an experimental animal, (*the blood supply to*

*the limbs was completely cut off*) and then prostigmin was given intravenously, there was a depression of the patellar jerk. However, with an intact general circulation no such phenomenon occurred. Schweitzer and Wright postulated a depressant action of the drug on the isolated spinal cord to account for their findings. They were careful to point out that a similar amount of prostigmin injected subcutaneously or intramuscularly had no such depressant effect on the reflexes. In a later study (1937) they found that when injected intravenously into un-atropinized animals in doses of 0.5 mg., prostigmin slightly "depresses the knee jerk, and may completely abolish it for many minutes in doses of 1 mg." With the circulation to the limbs cut off they found that 1.5 to 3 mg. of prostigmin injected into the jugular vein produced a diminution or abolition of the knee jerk. They conclude that, "As the peripheral action of prostigmin on muscle is excitant there can be no doubt from the above results that prostigmin exerts a direct inhibitory influence on the central nervous system."

Several points are at once obvious. With intravenous doses of 0.5 to 3 mg. in animals as a basis, a comparable amount in the human would be well above that generally used, and actually in the range of toxic peripheral depressant effects. In the paper by Kabat the maximal dose mentioned is 3 cc. (1.5 mg.) given *intramuscularly*, or 45 mg. by mouth three times a day. Absorption and utilization of prostigmin given orally is notoriously inefficient. Even by mouth, sensitivity occurs very frequently below the maximum level mentioned above. Neither intramuscular nor mouth administration meets the criteria of Schweitzer and Wright's experiments.

For these and other reasons, the experiment is not a critical one necessarily applicable to human physiology. It may be concluded that these interesting studies are insufficient to explain the reported effects of prostigmin on neuromuscular conduction in the various syndromes mentioned above. Nevertheless, reports of the excellent results achieved with this form of therapy make further study imperative. Unfortunately, there has been opportunity for group study in only certain of the types of pathological conditions represented in the original reports.[63,64]

At the American Rheumatism Association Meeting in May, 1946, Balboni[65] and his associates presented their results in a large series of carefully observed patients with rheumatoid arthritis in various stages. They reported no useful therapeutic effect with long trials of prostigmin. Discussion on the floor unanimously supported their findings. The clinical data presented by a large group of investigators were overwhelmingly against any therapeutic value of the drug in the treatment of rheumatoid arthritis. Cohen and Trommer,[66] and also Kabat,[60] believe that chronic arthritic changes respond more favorably than acute. This is surprising since one ought logically to expect acute muscle spasm and early deformity to be easier to influence than long term contracture associated with fibrosis.

Increased utilization of prostigmin in the various syndromes described by Kabat and his group will ultimately define its clinical usefulness. Further laboratory investigation of its mode of action is likewise desirable.

### ANTIDOTAL NATURE OF ANTICHOLINESTERASES

It has been repeatedly demonstrated that the anticholinesterases, such as physostigmine and prostigmin, are in certain concentrations, physiological antagonists of curare.[67,68] When applied to the curarized or partially curarized striated muscle preparation, they will evoke a return of electrical and mechanical response. However, when curarization has progressed to intense cen-

tral effects, the anticholinesterases do not seem to act in this way, and may, indeed, increase the severity of the poisoning. Koppanyi and Vivino[69] have reported experiments delineating the limits of the antidotal action of these drugs and show that increasing their doses does not increase antidotal action beyond a certain point. The addition of ephedrine or tyamine specifically increases the neutralization effect in their experiments.

Pick and Unna[70] found that with levels of tubocurarine which abolished cortical electrical potentials in the frog, prostigmin restored motor activity but did not influence the cortical depression.

Prostigmin itself caused a similar drop in cortical potentials. They concluded that curare and prostigmin were antagonists in myoneural junction action but that their central effects were similar. On this basis, prostigmin would be contraindicated as an antidote in severe curare intoxication.

## CONCLUSION

The availability of a pure curare alkaloid, tubocurarine, has accelerated experimental and clinical exploitation of its unusual properties. Unquestionably, a great deal remains to be learned. The most pressing problem is clarification of its mode of action at the myoneural junction. A method of assaying blood levels is badly needed, as is further elucidation of its central versus peripheral effects, and its true relationship to the anticholinesterases.

## REFERENCES


1. Berqard, Claude and Pelonze. Récherches sur le curare. *Compt. rend. Acad. d. sc.*, 31: 533, 1850.
2. West, R. The pharmacology and therapeutics of curare and its constituents. *Proc. Roy. Soc. Med.*, 28: 565, 1935.
3. Benedikt, M. Positive Resultate zur Curare-therapie. *Wien. med. Presse*, 7: 791–806, 1866.
4. Jousset. Du curare au point de vue thérapeutique. *Bull. gén. thérap.*, 69: 294, 1865.
5. King, H. Curare alkaloids; 1. tubocurarine. *J. Chem. Soc.*, p. 1381, 1935.
6. Wintersteiner, O. and Dutcher, J. D. Curare. *Science*, 95: 3–10, 1942.
7. Ing, H. P. The curariform action of onium salts. *Physiol. Rev.*, 16: 527–544. 1936.
8. McIntyre, A. R. and King, Ray E. Contraction of denervated muscle produced by *d*-tubocurarine. *Science*, 97: 516, 1943.
9. Eccles, J. C., Katz, B. and Kuffler, S. W. Nature of the endplate potential in curarized muscle. *J. Neurophysiol.*, 4: 362–387, 1941.
10. Eccles, J. C. and Knuffler, S. W. Initiation of muscle impulses at the neuromuscular junction. *J. Neurophysiol.*, 4: 402–417, 1941.
11. Kuffler, S. W. Electrical potential changes at any isolated nerve-muscle junction. *J. Neurophysiol.*, 5: 18–26, 1942.
12. Kuffler, S. W. Further study of transmission in an isolated neuromuscular fibre preparation. *J. Neurophysiol.*, 5: 309–324, 1942.
13. Kuffler, S. W. Specific excitability at the endplate. *J. Neurophysiol.*, 6: 99–110, 1943.
14. Griffith, H. R. and Johnson, G. E. The use of curare in general anesthesia. *Anesthesiology*, 3: 418, 1942.
15. Mallenson, F. B. Curare in anesthesia. *Lancet*, 2: 75, 1945.
16. Whitacre, R. J. and Fisher, A. J. Clinical observations on the use of curare in anesthesia. *Ohio State M. J.*, 40: 1155, 1944.
17. Cullen, S. C. The use of curare for the improvement of abdominal muscle relaxation during inhalation anesthesia. *Surgery*, 14: 261, 1943.
18. Lundy, J. S., Tuohy, E. B., Adams, R. C., Mousel, L. H. and Seldon, T. H. Annual report for 1943 of the section on anesthesiology. *Proc. Staff. Meet., Mayo Clin.*, 19: 408, 1944.
19. Cole, F. The use of curare in anesthesia. *Anesthesiology*, 6: 48, 1945.
20. Borromea, Sister M. Intocostrin with pentothal sodium anesthesia. *Ann. Meet. Am. Assoc. of Nurse Anesthetists of Ill.*, March 22, 1945.
21. Shane, S. M. Curare—a complement to anesthesia. *Anesth. & Analg.*, 24: 256, 1945.
22. Brody, J. The use of curare in sodium pentothal-nitrous oxide-oxygen anesthesia. *Anesthesiology*, 6: 381, 1945.
23. Waters, R. M. Nitrous oxide-oxygen and curare. *Anesthesiology*, 5: 618, 1944.
24. Cullen, S. C. Clinical and laboratory observations on the use of curare during inhalation anesthesia. *Anesthesiology*, 5: 166, 1944.
25. Adams, R. C. Curare as an aid to relaxation in anesthesia. *Clin. North America*, 25: 735, 1945.
26. Griffith, H. R. and Johnson, G. E. Curare as an aid to the anesthetist. *Lancet*, 2: 74, 1945.
27. Ruskin, A., Ewalt, J. and Decherd, G. The electrocardiogram of curarized human patients. *Dis. Nerv. System*, 4: 335, 1943.
28. Bennett, A. E. Preventing traumatic complications in convulsive shock therapy by curare. *J. A. M. A.*, 114: 322, 1940.
29. Cummins, J. A. Metrazol complications as affected by the use of curare. *Canad. M.A.J.*, 47: 326, 1942.
30. Easton, N. L. and Sommers, J. Vertebral fractures in metrazol therapy with and without the use of curare as a supplement. *J. Nerv. & Ment. Dis.*, 99: 256, 1944.

31. Woolley, L. F., Jervis, J. R. and Ingalls, G. S. On the use of curare in modifying convulsive shock. *J. Nerv. & Ment. Dis.*, 96: 680, 1942.
32. Jones, G. L. and Pleasants, E. N. Curare modification of therapeutic convulsions. *Dis. Nerv. System*, 4: 17, 1943.
33. Harris, M. M., Pacella, B. L. and Horowitz, W. A. A study of the use of curare in metrazol convulsant therapy with some electroencephalographic observations. *Psychiatric Quart.*, 15: 537, 1941.
34. Pearlstein, M. A. and Weinglass, A. Total effects of prolonged complete curarisation. *Am. J. Dis. Child.*, 67: 360, 1944.
35. West, R. Intravenous curarine in the treatment of tetanus. *Lancet*, 230: 12, 1936.
36. Cullen, S. C. and Quinn, C. S. The use of curare in the treatment of tetanus. *Surgery*, 14: 256, 1943.
37. Spencer Wells, T. Three cases of tetanus in which "Woorare" was used. *Proc. Roy. Med. Chir. Soc., London*, 3: 142, 1858–61.
38. Hoffman, F. A. Ein Fall von Tetanus traumaticus mit Curare behandelt. *Berliner klin. Wchnschr.*, 16: 637, 1879.
39. Chesterfield and North Derbyshire Hospital. A case of traumatic tetanus which recovered under treatment by hypodermic injections of curare. *Lancet*, 2: 831, 1904.
40. Florey, H. W., Harding, H. E. and Fildes, Paul. The treatment of tetanus. *Lancet*, 227: 1036, 1934.
41. Cole, L. Treatment of tetanus by curare. *Brit. M. J.*, 1: 125, 1935.
42. Mitchell, J. S. A case of tetanus treated with curarine. *Lancet*, 228: 262, 1935.
43. Isacson, S. E. and Swenson, S. A. Curare in the treatment of tetanus. *Nebraska M. J.*, 26: 136, 1941.
44. Hanna, C. B. Use of curare in reducing convulsive effects of tetanus. *J. South Carolina M. A.*, 42: 5–8, 1946.
45. Bremer, Frederic, Titeca, J. and Van der Meiren, L. Effective action on the muscular tonus of small doses of curare. *Compt. rend. Soc. Biol.*, 96: 704, 1927.
46. Hartridge, H. and West, R. Parathyroid tetany in dogs and its abolition by curare. *Brain*, 54: 312, 1931.
47. Burman, M. S. Therapeutic use of curare and erythroidine hydrochloride for spastic and dystonic states. *Arch. Neurol. & Psychiat.*, 41: 307–327, 1939.
48. Bennett, A. E. Clinical investigations with curare in organic neurological disorders. *Am. J. M. Sc.*, 202: 102, 1941.
49. Denhoff, Eric and Bradley, Charles. Curare treatment of spastic children. *New England J. Med.*, 226: 411–416, 1942.
50. Romansky, M. J. and Rittman, G. E.: Method of prolonging action of penicillin. *Science*, 100: 196–198, 1944.
51. Schlesinger, E. B. The use of suspensions of tubocurarine in oil in the treatment of spasticity. *Arch. Neurol. & Psychiat.*, 55: 530–534, 1946.
52. Schlesinger, E. B. Recent advances in the use of curare in clinical practice. *Bull. N. Y. Acad. Med.*, 22: 529, 1946.
53. Lewis, Thomas and Kellgren, J. H. Observations relating to referred pain viscero-motor reflexes and other associated phenomena. *Clin. Sc.*, 4: 47, 1939.
54. Wolff, H. G. Some observations on pain. The Harvey Lectures, Series 39, 39–95, 1943–1944.
55. Crothers, Bronson. Disorders of the Nervous System in Childhood. Page 144. New York, 1926. D. Appleton & Co.
56. Ransohoff, N. S. Curare in the acute stage of poliomyelitis. *J. A. M. A.*, 129: 129–130, 1945.
57. Fox, M. J. Curare in the treatment of acute poliomyelitis. *J. A. M. A.*, 131: 278–280, 1946.
58. Kabat, H. and Knapp, M. E. The mechanism of muscle spasm in poliomyelitis. *Staff Meet. Bull., Hosp. Univ. Minnesota*, 14: 359–367, 1943.
59. Kabat, H. and Knapp, M. E. The use of prostigmin in the treatment of poliomyelitis. *J. A. M. A.*, 122: 989–995, 1943.
60. Kabat, Herman. Studies on neuromuscular dysfunction. VI. Neostigmin therapy of neuromuscular dysfunction. *Med. Ann. District of Columbia*, vol. 14, no. 6248, June, 1945.
61. Schweitzer, A. and Wright, S. The action of eserine and related compounds and of acetyl choline on the central nervous system. *J. Physiol.*, 89: 165, 1937.
62. Schweitzer, A. and Wright, S. Further observations on the action of acetyl choline, prostigmin, and related substances on the knee jerk. *J. Physiol.*, 89: 284, 1937.
63. Watkins, A. L., Brazier, M. A. B. and Schwab, R. S. Concepts of muscle dysfunction in poliomyelitis. *J. A. M. A.*, 123: 188–192, 1943.
64. Fox, M. J. and Spankus, W. H. The value of neostigmin in acute anterior poliomyelitis. *J. A. M. A.*, 128: 720–722, 1945.
65. Balboni, V. G., Hollander, J. L. and Kydd, D. M. Effects of prostigmine on the muscle spasm in rheumatoid arthritis. *Reunion Meet. Am. Rheumatism Assoc. N. Y.*, May 24–25, 1946.
66. Trommer, P. R. and Cohen, A. Use of neostigmine in treatment of muscle spasm in rheumatoid arthritis and associated conditions. *J. A. M. A.*, 124: 1237, 1944.
67. Fegler, J. and Kowarzyk, K. Reciprocal antagonism between physostigmine and curare. *Compt. rend. Soc. Biol.*, 127: 1149, 1938.
68. Mautner, H. and Luisada, A. Antagonistic effect of asphyxia to curare paralysis of the vagus nerve. *J. Pharm. & Exper. Therap.*, 72: 386, 1941.
69. Koppanyi, T. and Vivino, A. E. Prevention and treatment of *d*-tubocurarine poisoning. *Science*, 100: 474, 1944.
70. Pick, E. P. and Unna, K. The effect of curare and curare-like substances on the central nervous system. *J. Pharmacol.*, 83: 59, 1945.

# Seminar on Antibiotics

## Chemotherapy and Antibiotics in the Treatment of Meningitis

YALE KNEELAND, JR., M.D.*
NEW YORK, NEW YORK

In the history of medical therapeutics there have been few more dramatic events than the influence of chemotherapy and antibiotics on purulent meningitis. A decade ago cerebrospinal fever, in spite of specific serum therapy, was still a grave disease with a high case-fatality rate. Meningitis due to H. influenzae was almost invariably lethal, and recovery from pneumococcal or streptococcal meningitis unknown. Now, as a result of new agents in treatment, cerebrospinal fever is a brief disease, usually without sequellae, and carrying an almost negligibily small case-fatality rate; moreover, recovery from the other varieties of purulent meningitis can occur in the majority of cases. These results, of course, have been achieved by sulfonamides, penicillin and streptomycin, but they cannot be approximated without a considerable knowledge of the diseases in question, together with technical skill in management. It is the purpose of this review to discuss the technics of these new treatments.

### CEREBROSPINAL FEVER (MENINGOCOCCAL MENINGITIS)

Cerebrospinal fever is the commonest of the so-called primary meningitides. In this instance the use of the term "primary" is a poor one, for the meningitis is often preceded by a well defined catarrhal and septicemic state. One speaks of it as primary merely to differentiate it from a condition like pneumococcic meningitis, which is ordinarily secondary to lesions such as skull fracture, mastoiditis, etc.

The causative agent of cerebrospinal fever, *N. meningitidis*, is an organism which has a peculiar predilection for the coverings of the brain and spinal cord. It is not particularly pathogenic for the upper respiratory tract. It can be recovered on culture from the nasopharynx of healthy carriers who have never had the disease, and under normal conditions, when the disease is not epidemic, such healthy carriers may be as high as 5 per cent of urban populations. Presumably the appearance of sporadic cases is due to this fact; either the healthy carrier himself contracts the disease, or else he passes on the organism by expelled droplets to another individual whose resistance is sufficiently low so that invasion occurs. In either case, implantation in the meninges takes place by way of the blood stream, and this may or may not take the form of a clearly defined septicemia with fever, purpuric rash and a positive blood culture. Sporadic cases are seen in all large cities during the winter months, and the case history will yield no clue as to the source of the infection. In contrast to this, the disease may also take on epidemic proportions, particularly under circumstances

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York.

when large groups of susceptibles are herded together. As susceptibility decreases with age, it follows that localized outbreaks are most often seen in institutions for the young, Army camps, and the like. At such times, bacteriological surveys have shown that the carrier-rate becomes very high. The clinical severity of the disease varies in different years and different epidemics, and it was observed in the days of serum treatment that the case fatality rate varied rather widely even when potent anti-serum was employed.

These epidemiological findings have been briefly sketched in to emphasize the fact that cerebrospinal fever may occur anywhere and at any time. Unless every physician bears this constantly in mind, patients will continue to die needlessly of meningitis, for the key to success in this disease is *early diagnosis together with prompt and vigorous treatment*. And the only means of early diagnosis is to suspect meningitis in every patient who is taken acutely ill. This may sound like a rather extravagant statement, but it is the author's conviction that priceless time is continually being lost, not because physicians are ignorant of the florid picture of the disease, but because the more subtle, early danger signals escape notice simply owing to the doctors' failure to think of meningitis. This is not the place for a systematic consideration of the signs and symptoms of the disease, but a few points in regard to early diagnosis are worthy of mention. First, it must be borne in mind that meningococcic infections almost invariably provoke a leucocytosis. Now, apart from lobar pneumonia and streptococcal throat infections (the nature of which should be fairly obvious) the vast majority of ordinary acute febrile diseases are *not* accompanied by a leucocytosis. Thus, a young individual who has a chill followed by fever, a macular rash tending to become purpuric, and a high white blood count, is almost certainly in the septicemic stage of cerebrospinal fever. It is *not* measles. If treatment is delayed until frank meningeal signs appear, very valuable time will be lost. Even in the absence of the characteristic exanther of cerebrospinal fever, the disease must always be considered a possibility in acutely ill young people showing a leucocytosis. Now it is obviously impractical to do a blood count on all cases of common respiratory infections during the winter months. But if certain warning signals are kept in mind, blood counts will be done where needed. These are as follows: repeated vomiting, very severe headache, mental dullness and confusion should put the doctor on the alert. These symptoms are *not* characteristic of common upper respiratory infection, and they are indications for a leucocyte count. They are also indications for a very careful search for meningeal signs and a lumbar puncture, if any grounds for suspicion exist.

The meningococcus is exceedingly sensitive both to sulfonamides and penicillin, but in deciding how these agents are to be used, singly or in combination, certain elementary facts must be remembered. Sulfonamides (of which sulfadiazine is probably the drug of choice) are easy to administer, and they penetrate into the cerebrospinal fluid in high concentration. They may, however, produce dangerous side effects. Moreover, there is a time lag of a few hours before they begin to exert their influence. Penicillin, on the other hand, probably begins its action more promptly and it is almost wholly non-toxic. But unless given in enormous doses parenterally, comparatively little makes its way into the subarachnoid space. It is generally agreed, therefore, that in meningitis it must be given intrathecally, and this naturally implies repeated lumbar taps. With this background, let us consider the ideal treatment of the disease.

This writer believes that sulfadiazine, because of its great efficacy (as shown in many thousands of patients treated in the Army with this drug alone), its ease of administration, and high penetration into the cerebrospinal fluid, still remains the most valuable single agent in cerebrospinal fever. That penicillin also has a place of great importance is equally true, and this point will be made clear in the ensuing consideration of several clinical categories of disease.

*Mild to Moderate Cases Treated Early.* A very wide experience indicates that sulfadiazine alone is wholly adequate in the treatment of this variety of case. An outline of treatment is as follows: Lumbar puncture for diagnosis; fluid to be sent for cell count, smear, culture, sugar; blood culture. Immediately after these are completed, give 5 Gm. of sodium sulfadiazine dissolved in a liter of normal saline by fairly rapid intravenous infusion. As the patient is often somewhat dehydrated, this may well be immediately followed by more intravenous fluid at a slower rate. If sodium lactate is available, 500 to 1000 cc. of a 1/6 molar solution may be administered in the second infusion in order to achieve a rapid alkinization of the urine; for it must be remembered that where sulfonamides are employed in large dosage, the danger of precipitation in the urinary passages is not inconsiderable. It also goes without saying that the usual alertness to the possibility of toxic side effects must be maintained with repeated observations of the blood count and urine.

The object of treatment with sulfadiazine is the rapid establishment and maintenance of a satisfactory blood concentration of the drug, preferably in the range of 12 to 15 mg. per cent. The only way this can be determined is by having the blood level estimated, a procedure which, in a serious infection like meningitis, is well worth carrying out. By our initial infusion we have probably achieved this level. Let us estimate it, say, at six or eight hours after the beginning of treatment, and guide our future dosages accordingly. If at this time the patient can take medication by mouth, it can be continued in the form of 1.0 to 1.5 Gm. (or even higher if necessary) every four hours. The customary forcing of fluids should be employed, and 2.0 Gm. of soda bicarbonate may be given with each dose of sulfadiazine to maintain urinary alkalinity. The drug, of course, can be continued by the intravenous route, but in the majority of mild cases the single initial infusion will suffice.

The expected result with this treatment is a noticeable improvement in clinical symptoms usually perceptible six to twelve hours after therapy is instituted. In twenty-four hours there is usually marked improvement and the fever has diminished. Stiff neck will ordinarily persist for two to three days, but at the end of forty-eight hours the patient should be otherwise asymptomatic. Failure to obtain this result usually means that dosage has been inadequate, although the possibility of an accelerated sulfonamide reaction in a sensitive individual must be kept in mind.

Treatment with sulfadiazine alone then, in the mild to moderate case, is simplicity itself. A satisfactory drug level is established and maintained, together with the usual sulfonamide precautions. One or two other points deserve comment, however. The first is the duration of treatment. While it is probable that cure of the disease takes place very rapidly, it is best to maintain treatment longer than may be strictly speaking necessary. A week is, in my opinion, the minimum. The second point relates to lumbar punctures. It is my belief that after the first diagnostic tap, lumbar puncture need be performed for only two reasons, the relief of symptoms (persistent headache, vomiting, nuchal rigidity, respiratory difficulty),

or to appraise the meningeal situation in a case in which the expected good result apparently has not been achieved. In other words, the majority of patients can be handled quite satisfactorily with but the single initial diagnostic tap.

This is a brief outline of treatment of the ordinary case of cerebrospinal fever with sulfadiazine alone. The majority of patients can be treated in this way. Before going on to discuss the more severe types, it is worth mentioning that in an occasional mild case of cerebrospinal fever sulfadiazine may be contraindicated. The aged sometimes tolerate the drug rather poorly; in the presence of renal insufficiency, extra caution must be employed with sulfadiazine; these are indications of the type of case in which a physician may prefer to use penicillin alone, as he most certainly would if dealing with a patient known to be sensitive to sulfadiazine.

*Severe Cases, or Cases in Which Treatment Has Been Delayed.* By these terms are meant either a patient with an unusually violent onset, early delirium, stupor, etc., or one who has evidently been in the meningitic stage for some considerable period of hours before treatment can be started. It may be remarked that before the advent of penicillin, large numbers of patients in these categories were cured by sulfadiazine alone. With the antibiotic at hand, however, there are theoretical as well as practical indications for its use. An intrathecal injection of penicillin should be made through the lumbar puncture needle immediately after withdrawal of the fluid for diagnostic study. It is probably wise not to exceed 25,000 or 30,000 units; this may be dissolved in 4 or 5 cc. of saline and injected slowly and gently, with intermittent withdrawal of spinal fluid into the syringe so that further dilution is effected. At the same time, if there are marked evidences of septicemia, a arge dose, say 200,000 units, may be given intramuscularly. Meanwhile, sulfadiazine treatment is instituted and maintained as in mild or moderate cases. If it is deemed necessary to repeat the lumbar tap later for symptomatic relief, a second intrathecal injection of penicillin may be made. It might be wise also to repeat the intramuscular injection after three hours. Thenceforward the patient may be carried on sulfadiazine alone. By these means, the full immediate effect of penicillin is obtained both locally and systemically during the latent period before the sulfonamide begins exerting its effect.

*Maximally Severe Cases (Waterhouse-Friderichsen Syndrome).* The so-called Waterhouse-Friderichsen syndrome consists of a state of shock accompanying profound sepsis. It is most often seen in overwhelming meningococcic infection. Clinically, it is characterized by the sudden appearance of a profuse purpura together with very low blood pressure, at shock level, tachycardia, anuria, etc. In addition, infection of the central nervous system has ordinarily taken place, and one usually sees delirium or coma with some meningitic signs. Here is a medical emergency in which time is of the essence, and there is no doubt that an occasional case conforming to this pattern will be lost in spite of the best possible care. On the other hand, there are now abundant examples of the so-called Waterhouse-Friderichsen syndrome, hitherto regarded as a condition utterly without hope, in which recovery has taken place with modern treatment.

One may repeat, time is of the essence. A large intramuscular dose of penicillin should be given as the patient is being prepared for lumbar puncture. The treatment of the infection proceeds along the lines suggested for severe cases, except that intramuscular penicillin in large doses should be continued at three-hour intervals for two or three days, and that higher blood levels

of sulfadiazine, i.e., around 20 mg. per cent, should be aimed at. It is also probably wise to repeat lumbar punctures with intrathecal antibiotic twice daily for a couple of days. But there is an additional indication for treatment here of the utmost importance, i.e., the treatment of shock. For this purpose it will probably be necessary to employ transfusions of blood or plasma, and if the blood pressure is not materially restored by the initial intravenous infusion of sulfadiazine in saline, either whole blood or plasma should be given immediately. These measures should be repeated later if necessary.

In cases of this sort the question usually arises, should adrenal cortical hormone be given? This is based on the frequent association noted at the postmortem examination of massive adrenal infarction with the Waterhouse-Friderichsen syndrome. It seems to me, however, that one does not need to explain the shock on the basis of adrenal insufficiency. For one thing, it comes on too fast. For another, many cases have been described in which profound shock occurred in the presence of a comfortable supply of anatomically normal adrenal tissue. My own belief is that this debate is an academic one. Most certainly, patients with the Waterhouse-Friderichsen syndrome have survived when the shock was treated by simple methods. Equally certain is it that the patient will ultimately die if all his adrenal tissue has been destroyed. However, adrenal cortical hormone will probably do no harm and may be used.

The foregoing paragraphs are intended to outline a more or less ideal scheme of treatment of various categories of cerebrospinal fever. By the use of such methods, in circumstances in which early diagnosis is feasible, the case fatality rate can probably be reduced to less than 2 per cent. It was about 2 per cent for the year 1944 in the United Kingdom Base among American soldiers, and no doubt this figure can be somewhat improved. One additional point is of sufficient interest to warrant mention. So great is the sensitivity of the meningococcus to sulfadiazine that one or two small doses are sufficient to eliminate the carrier state. Thus, when cerebrospinal fever breaks out in a dense population, such as an Army camp, a few small prophylactic doses administered to the whole command will arrest the epidemic at once.

### PNEUMOCOCCUS AND HEMOLYTIC STREPTOCOCCUS MENINGITIS

These conditions will be considered next because their treatment is so similar to that of cerebrospinal fever. It is essential first, however, to speak of an important difference in pathogenesis. As has been indicated above, cerebrospinal fever is a "primary" type of meningitis, i.e., it is not secondary to an adjacent or remote suppurative process, although it is preceded, presumably in all cases, by blood involvement, even if this be not apparent. On the contrary, in pneumococcal and streptococcal meningitis, the physician must be constantly on the look-out for a focus which may need surgical therapy. Both diseases may arise secondarily to a simple septicemia, but they are more likely to occur as a result of a contiguous lesion. Fractures through the base of the skull entering a contaminated sinus are examples of this. Otitic infection, usually with mastoiditis, is another. Occasionally, they arise following suppurative sinus disease. There is always the possibility of an associated suppurative lateral or cavernous sinus thrombosis. Brain abscess may coexist. Now local areas of suppuration such as these are not very favorably affected by parenteral sulfonamide or antibiotic treatment; and, if they continue to feed organisms into the meninges, treatment will not avail. They must be searched for, located and drained. It follows, therefore, that an

internist who is treating meningitis due to either pneumococcus or streptococcus will almost always need the collaboration of an otologist and occasionally of a neurosurgeon.

There is another point of difference which bears on the treatment. Both of these organisms produce a much more severe miningitis, apart from the associated lesions, than does the meningococcus. Even before any specific therapy there were some recoveries from cerebrospinal fever; perhaps 20 per cent survived the disease though often with permanent sequellae. This did not occur with pneumococcus or streptococcus. Pathologically, they produce a more severe lesion. The exudate is more abundant, more plastic. Fibrin formation is marked, with a great tendency to blocking of aqueducts and foramina. There is also a rather marked tendency to perivascular inflammation, extending down into the brain substance, with vascular thrombosis, which does not usually occur in cerebrospinal fever. These facts have an important bearing on our thinking in regard to the intensity and duration of treatment.

*Pneumococcic Meningitis.* The technics of sulfadiazine and penicillin therapy are the same as in severe cerebrospinal fever except that they are employed more intensively and for a longer period. Thus lumbar punctures with local injection of penicillin should be done twice daily for a week, and once daily for the next week. Penicillin in 200,000 unit doses intramuscularly every three hours should be continued for two weeks, although the dose may be cut in half at the end of the first week if the patient is doing well. Sulfadiazine levels of 15 mg. per cent are maintained. As to duration of treatment, there can be, of course, no set rule. But it seems a wise general principle to maintain it much longer than seems necessary. My inclination is to keep up local and parenteral penicillin for two weeks, and sulfadiazine for an additional week, if tolerated. (If not, intramuscular penicillin should be kept up for that period.) After all, we are dealing here with a very grave and treacherous disease, and one in which relapses have been observed when treatment has been discontinued too soon.

Another question which is sure to arise is whether to give of type-specific antipneumococcus serum. My own feelings on this point might be indicated as follows: If an immediate typing has been made from the spinal fluid so that one knows the type at the very outset, if a supply of highly purified rabbit serum of the appropriate type is at hand, if the clinical picture is extremely grave, I am inclined to give a single intravenous dose. Usually these requirements are not met, however. There is apt to be a considerable lapse of time before one can give this treatment. Then, if the patient appears to be doing well, I am disinclined to risk an immediate serum reaction or serum disease later to complicate the picture during convalescence.

It has been suggested that the use of an anticoagulant, such as heparin, might be indicated with a view to lessening fibrin formation on the coverings of the brain. From a theoretical point of view this notion has much in its favor. But it must be remembered that heparinization will greatly complicate an already complicated problem in therapeutics, and that it must be interrupted if any surgery is undertaken, which is apt to be the case. I have seen one or two patients so treated with success, but there are a great number of equally successful cases in which no anticoagulant has been used.

One object of the anticoagulant, obviously, is to prevent block in the circulation of the cerebrospinal fluid. Should this complication develop in any type of meningitis, it is probably too late for heparin to be effective. Under these circumstances the condition should be promptly recognized

and an endeavor made to treat the internal hydrocephalus by cistern and ventricular punctures, as indicated, and the instillation of antibiotic by these routes.

With the introduction of the first sulfonamide effective against the pneumococcus (sulfapyridine) the first reports of cure of pneumococcic meningitis began appearing in the literature. With the use of this agent alone, perhaps 20 per cent of patients might be expected to survive. By means of the combined penicillin-sulfadiazine regimen of the type outlined above, the percentage has materially risen. It may now be in the neighborhood of 75 per cent.

*Hemolytic Streptococcic Meningitis.* The same principles apply here as in pneumococcic meningitis. Streptococcic meningitis is, however, a somewhat milder disease, and the intensity of the treatment may be lessened without danger. With sulfonamide alone the recovery rate was about three times as high as in pneumococcic meningitis. It would seem justified, therefore, to advise a slightly less vigorous regimen. Lumbar punctures may be done daily for a week with injection of penicillin, and then omitted if the clinical course warrants. Penicillin might be given in 100,000 unit doses every three hours after the first day. But I should be inclined to keep it up for a fortnight and the sulfadiazine for three weeks, as in the case of the pneumococcic infection.

### H. INFLUENZAE MENINGITIS

Unlike the two varieties just discussed, H. influenzae meningitis is not usually associated with trauma or a nearby suppurative focus. It, therefore, may be described as "primary," although some degree of pharyngitis probably precedes infection of the meninges. Thus it resembles cerebrospinal fever clinically except that the rash, frequently seen in the latter condition, does not occur, and careful bacteriological examination of the fluid is necessary to differentiate the two. H. influenzae meningitis is almost wholly limited to infants and young children and is by no means uncommon. In fact, it has been stated to account for nearly a quarter of all the purulent meningitis in this age group. It was early recognized that the influenzae bacilli causing meningitis showed more serological specificity than the common respiratory strains, but it remained for Pittman[1] to demonstrate that meningeal organisms were encapsulated, and fell into well defined type-specific groups. It is now known that nearly all H. influenzae meningitis is caused by a type designated by Pittman as "b." These discoveries led to the therapeutic trial of specific antiserum. Early endeavors in this direction with horse serum were not very successful. The great advance in serum therapy was made by Alexander when he introduced highly concentrated type-specific rabbit antibody solution. At about the same time it was noted that sulfonamides had an action against H. influenzae. Of the sulfonamides, by far the best is sulfadiazine. The ideal treatment, as worked out by Alexander, consisted in a combination of the two agents.

H. influenzae meningitis is almost exclusively a problem in pediatrics, and for the complete description of Alexander's combined serum-sulfadiazine treatment the reader is referred to her most recent paper.[2] Essentially, it consists in the parenteral administration of 0.1 Gm. of sulfadiazine per kg. of body weight, accompanied by the intravenous administration of a single dose of antibody solution. The dosage of this is regulated by the severity of the infection (as judged by spinal fluid sugar levels), and ranges from 25 to 100 mg. of antibody nitrogen. The sulfadiazine is repeated at twelve-hour intervals until the patient can take the drug by mouth. By this method the case fatality rate was reduced to about 25 per cent in quite a large series of cases.

Since these advances were made a new antibiotic, streptomycin, has been introduced, which is effective against many gram-negative organisms insensitive to penicillin. Among these is H. influenzae. Streptomycin has, therefore, been tried in the treatment of influenza bacillus meningitis with very encouraging early results. Final appraisal of the drug is yet to be made, but Alexander's present scheme of therapy is as follows:[3]

As soon as the diagnosis is made—and here again one must repeat that accurate bacteriological study of the spinal fluid is *essential*—the child is started on streptomycin. In mild to moderately severe cases, this is the only form of treatment used (by mild to moderately severe is meant those patients with spinal fluid sugar over 15 mg. per cent). The drug is administered both intramuscularly and intrathecally, the twenty-four-hour dosage in the former category being 20,000 units per pound of body weight; this is divided into eight doses injected at three-hour intervals. By the intrathecal route 25 to 50 thousand units in a volume of about 5 cc. are given daily.

If the case is clinically very severe, or if the spinal fluid sugar is below 15 mg. per cent, combined serum-sulfadiazine treatment is given in addition to the above. So also are all three agents to be used if a good result is not obtained by streptomycin alone, or if the organism should develop streptomycin resistance. From early observations on this method of treatment it seems likely that the case fatality rate in H. influenzae meningitis will be still further materially reduced.

## OTHER VARIETIES OF PURULENT MENINGITIS

The four micro-organisms discussed above cause in the aggregate the great majority of cases of purulent meningitis. It is quite rare for infection of the meninges to be due to other bacteria. And yet virtually every pathogenic organism has at one time or another been described as causing meningitis. It is, let me repeat, for this reason that careful bacteriological study of the spinal fluid is so essential. The treatment of other types of purulent meningitis is dependent on a knowledge of the organism in question and follows the lines already described; that is to say, large doses of parenteral sulfadiazine are given—assuming the organism has any sensitivity to it—and the appropriate antibiotic is administered by the intrathecal and intramuscular route. As in the case of pneumococcis meningitis, it is probably wise to maintain treatment for a long period of time.

## REFERENCES

1. Pittman, M. *J. Exper. Med.*, 53: 471, 1931.
2. Alexander, H. E. *J. Pediat.*, 25: 517, 1944.
3. Alexander, H. E. Personal communication.

# Conference on Therapy

## Treatment of Coronary Artery Disease

### (Concluded)*

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and the New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy by The Macmillan Company. The next report will appear in the January, 1947 issue and will concern Treatment of Rheumatic Fever.

DR. HARRY GOLD: We had a session on the treatment of coronary artery disease last week. There was not time enough to consider as many of the questions in need of an airing as we had hoped. It is for this reason that we are now holding the second conference on the same subject.

We had been having all the discussion from the front rows. How about the back rows today?

INTERNE: What is your opinion about the length of time one should keep patients with coronary thrombosis in bed?

DR. GOLD: Dr. Pardee, how long should patients with coronary thrombosis remain in bed?

DR. HAROLD E. B. PARDEE: It depends on the individual patient. It is about six weeks for most of them. There are some, however, who are so seriously ill that complete rest for a longer time is necessary. There are still others whose attack is obviously so mild that they may be allowed out after four weeks.

DR. GOLD: You do not sit them up in a chair in two weeks?

DR. PARDEE: I do not. I would not consent to the patient getting out of bed. I have occasionally allowed patients to get out of bed so early against my better judgment, because there seemed to be nothing else to do and there was no harm from it. That is, of course, in cases of a minor attack.

DR. GOLD: Do you not think that the patient sometimes has a pretty hard time of it on a bed pan and struggles more there than on a commode?

DR. PARDEE: Yes, I do let him use the commode under those circumstances.

DR. GOLD: It is a fact then, that you do sometimes get them up out of bed at the end of five or six days, is it not?

DR. PARDEE: Yes, but that is not the same as having the patient out of bed all the time.

DR. CARY EGGLESTO[redacted]ink it is a very important point that D[redacted]Gold makes about the strain of using a bed pan. That differs with different individuals. But, there are many to whom, in my opinion, the strain of using the bed pan is immeasurably greater and more trying than the commode at the side of the bed. Under such circumstances, I surrender to the commode promptly.

DR. HAROLD J. STEWART: You would feel much worse if a patient died on a commode than if he died on the bed pan because he was out of bed.

DR. GOLD: There is indeed the problem implied in Dr. Stewart's remark. However, the fact remains, as pointed out in one of

* From the Departments of Pharmacology and Medicine, Cornell University Medical College and The New York Hospital, New York City.

the previous conferences, that sitting in a chair involves no more burden on the heart than lying in bed, and it offers many advantages. The prejudice in favor of the bed has the support of long tradition and is difficult to overcome, but I firmly believe that the chair deserves a more prominent place in the management of the problems of acute coronary thrombosis.

DR. GOLD: Dr. Eggleston, what proportion of the patients with coronary thrombosis that you see, do you treat from beginning to end without a single drug, morphine or anything else?

DR. EGGLESTON: Virtually none.

DR. GOLD: You give them all morphine?

DR. EGGLESTON: No, but the vast majority of them get morphine.

DR. GOLD: Even if they do not have pain?

DR. EGGLESTON: In the acute stage, I think that the majority of patients require an opiate. In the first place, they are scared even if they have no very severe pain, and the calming influence of an opiate seems to me unequalled by any of our other sedatives. Therefore, I usually give them one or two doses of an opiate, and I prefer morphine or one of the other purified alkaloids.

DR. GOLD: It is my impression that in patients with coronary thrombosis doctors have gone to an extreme in the use of morphine. They often give it as a routine even when the patient is symptom-free. The doses are often too large. The intervals between doses are too short. The length of time doses are continued is too long. The result is an unjustifiable amount of morphine poisoning and dependence, vomiting, distention, urinary retention, respiratory depression, confusional states and the various other disturbances associated with this group of drugs. One should not give more than 15 mg. (¼ gr.) intramuscularly as the first dose and at least one-half hour should elapse between doses. The larger the dose the more likely it is to cause vomiting and this involves the very type of violent muscular activity we go to so much trouble to avoid in the acute phase. More than a total of 60 mg. (1 gr.) is rarely, if ever, justified on the first day. If that fails to abolish the pain, larger doses will also fail to do so, but will tend to induce a state of coma with dangerous respiratory depression. It is disconcerting to begin treating a patient for coronary thrombosis and to end by treating him for morphine poisoning. I think that situation is not rare. I have also seen some ambulant patients after an acute coronary episode going along with one or more daily doses of pantopon, dilaudid or spasmalgin. The difference in name seemed to have lulled the physicians into a false sense of security, or perhaps they were not aware of the fact that these represent morphine or its equivalents. Those that I saw were all addicted.

DR. EGGLESTON: I agree fully. I stop the morphine just as soon as pain and great anxiety disappear, and I substitute for the morphine one of the non-opiate hypnotics if they cannot sleep or if they are restless.

DR. GOLD: I believe that in general, not only morphine but other sedatives are used too freely in patients with coronary thrombosis. To keep them in a state of prostration, stupor or confusion by these agents seems to me a source of harm rather than good. Let them be without drugs if they are substantially free of symptoms.

INTERNE: Has demerol a place in the treatment?

DR. PARDEE: I have not as much faith in demerol as I have in morphine. Therefore, I have not used it in these cases. I have used demerol in other types of cases, and there I formed an opinion that it is less effective than morphine.

DR. GOLD: There is no doubt that demerol relieves pain and does so well in many cases of coronary thrombosis in doses about 7 to 10 times that of morphine, about 100 to 150 mg. of demerol in the place of

15 mg. of morphine. The two drugs, however, are not fully interchangeable. I know of one situation in which the patient, subject to severe and frequently recurrent attacks of cardiac pain, which were not relieved by nitroglycerin, secured prompt relief for a few hours from 100 mg. of demerol subcutaneously. He continued to use it quite frequently during a period of about two years and acquired both a tolerance and dependence. In one attack he took 100 mg. every hour for 5 doses which brought no relief but caused marked unrest. A dose of 15 mg. of morphine subcutaneously provided prompt relief in this situation. He had always avoided morphine because it invariably produced urinary retention requiring catheterization. Remember, demerol has a potentiality for addiction.

DR. MCKEEN CATTELL: I would like to ask whether anyone here uses drugs to prevent premature beats or ventricular fibrillation, since that is apparently a serious aspect of coronary occlusion. Do you ever use aminobenzoic acid or some of its esters, which have been shown to decrease the liability to ectopic rhythm in the case of various drugs, such as epinephrine, ether, chloroform?

DR. GOLD: Dr. Stewart, have you any opinion about that?

DR. STEWART: No.

DR. GOLD: Dr. Pardee, do you do anything to prevent ectopic rhythms in a patient with coronary thrombosis?

DR. PARDEE: I usually give a fair amount of atropine sulfate with the initial morphine, that is, 0.8 mg. ($\frac{1}{75}$ gr.). I do not repeat that unless an arrhythmia appears. In such patients, I continue the atropine 0.6 mg., at about four-hour intervals. There is good experimental work which shows that atropine decreases the tendency to ventricular fibrillation. Quinidine has been recommended for that purpose. It seems to me too depressing to the myocardium for use in such seriously defective hearts. It has also been said to produce ventricular fibrillation. I think it is rather an unsatisfactory drug.

DR. GOLD: I wonder if we could have a little more discussion of atropine in coronary disease. The report by LeRoy and Snider of Chicago in the *J. A. M. A.* of December 13, 1941, is frequently quoted. After a given degree of coronary occlusion in dogs, 75 per cent died, presumably from ventricular fibrillation. The mortality was reduced to 35 per cent in the group which received atropine in doses of 0.1 mg. per Kg., which is equivalent to about 6 mg. or $\frac{1}{10}$ gr. for a man. They then go on to advise giving a dose of 0.8 mg. or 0.013 mg. per Kg. intravenously to a man to relieve coronary spasm in association with coronary thrombosis. They refer to the doses in the dog and in man as equivalent, although in terms of body weight, the dose advised for man is only about one-eighth of that which protected the dogs. Do these results with massive doses in dogs apply to the small doses in man? I think it is one of the very common sources of error in therapeutics, that the results of animal experiments with massive doses are applied directly to small doses in humans.

DR. PARDEE: Do you think the 0.8 mg. dose of atropine is an effective dose in man?

DR. GOLD: It is not enough to block the cardiac vagus completely. In our studies we found that 2 mg. of atropine sulfate intravenously sends the ventricular rate in auricular fibrillation up as far as it will go. Larger doses send it up no further. We may then take about 0.03 mg. per Kg. as the dose of atropine which blocks the cardiac vagus in man. According to Pilcher and Sollmann's work of 1914, the susceptibility of the dog is fairly similar, about 0.03 mg. per Kg. being required to abolish the cardiac slowing response to vagal stimulation. We should have an answer to the question whether such doses in the dog would reduce

the mortality from coronary occlusion before we use the dog experiment as a basis for the routine use of atropine in man, since it is quite out of the question to give humans the large doses which were used in dogs.

DR. PARDEE: There is another aspect to atropine. You cannot use it continually in this dose of 0.8 mg. without the patient becoming very dry and uncomfortable, and so it is eliminated as a drug for use in a chronic disease like angina. I think it is an unpleasant medicine to give and I do not give it unless there is definite evidence of myocardial irritability.

DR. GOLD: I should say that these very large doses of atropine amounting to about 3 or 4 mg. per day not only make them uncomfortable but quite wretched, and cause extreme dryness of the mouth and skin, absence of sweating, blurring of vision, weakness of the bladder with disturbance of urination, and sometimes confusion and delirium. The proof of its value should be better than it is before I would be inclined to add these burdens to the patient ill with a coronary thrombosis.

Do you give it, Dr. Eggleston?

DR. EGGLESTON: Very little. I sometimes use papaverine when signs of cardiac arrhythmia appear.

DR. GOLD: Papaverine is another drug which needs to be examined critically. Katz and his associates, of the Michael Reese Hospital, revived this drug and have given it quite a boost in their reports since 1941. They found it highly effective against the anginal syndrome in oral doses of 1½ gr. 3 times daily. They also found it effective in controlling premature beats in oral doses up to 3 gr. 4 or 5 times a day, and a similar result in premature beats after 1 to 1½ gr. intravenously, this lasting, however, only two to ten minutes. Papaverine possesses many of the actions of quinidine, with which it has some chemical kinship, both having the quinoline nucleus. Like quinidine in animals, it diminishes the irritability and conductivity of the heart, prolongs refractory time, may cause A-V and intraventricular block, cardiac arrest, premature beats, coupling, ventricular tachycardia and fibrillation, and may prevent ventricular fibrillation resulting from cardiac stimulation. Papaverine relaxes blood vessels, increases coronary flow and produces a sedative action on the brain. Among the reasons why these authors prefer it to quinidine are its "powerful long-lasting direct coronary dilator action;" . . . "it may be given intravenously in large doses with a wide margin of safety;" . . . "it does not cause the toxic signs sometimes resulting from quinidine;" . . . "it is not a myocardial depressant."

It is easy to be carried away by such statements of advantages, and I know that many have been and are using it as freely as a totally innocuous drug. I have found it of equivocal value to control the pain of angina of effort in oral doses of 1½ gr. 3 times daily. The experimental literature showing the wide variety of toxic effects on the heart, the high concentrations necessary to dilate coronary vessels and the brief duration of these effects give me very little encouragement. In one group of heart perfusion experiments in the dog the increased coronary flow lasted only seven to sixty minutes with an average of twenty-one minutes, and the smallest dose was equivalent to an intravenous injection of 5 Gm. (45 gr.) in man, which, of course, one could never give. In the May, 1940, issue of the *American Heart Journal*, Essex and collaborators reported a marked increase in coronary blood flow in the trained dog after about 1.25 to 1.75 mg. of papaverine per Kg. intravenously. That is in the range of human intravenous dosage, but the effect only lasted two to three minutes. In this connection it has also been shown in the

dog, that a dose as small as the equivalent of about 3 gr. intravenously for man, may cause a 40 mm. fall of the blood pressure. I wonder how safe that would be in the patient with coronary thrombosis. We should also note that to control ventricular fibrillation in the intact dog fairly large doses were used, and the concentrations found necessary in heart perfusion experiments were equivalent to about 15 Gm. of papaverine in the blood of a man. As to the "wide margin of safety," I should call your attention to the fact that toxic rhythms have been reported from papaverine after doses well within the therapeutic range, namely, premature beats and coupled rhythm, and ventricular tachycardia, after an intravenous injection of 1 gr., and partial A-V block after 1½ gr. An oral dose of 3 gr. several times daily may cause sufficient drowsiness to require interruption.

I have an idea that papaverine has some value in coronary disease. How much, has yet to be established. Whether it is superior to quinidine has also to be established. Papaverine does not appear to possess the power to control auricular fibrillation. It certainly is not free of dangers.

I think it is worth while noting that in this conference very few drugs have been recommended for the treatment of angina of effort. Dr. Stewart last week referred to the controlled study of Riseman. I have here a group of papers by Riseman and associates of Boston, which indicate a dozen or more drugs as quite effective. One would judge that there was room for a good deal of choosing among drugs for the control of the cardiac pain. That is not in accord with my experience. Here is a paper in the July, 1937, issue of the *Archives of Internal Medicine*, which shows that nitroglycerin provided improvement in about 60 per cent of the patients, quinidine sulfate in about 40 per cent, aminophylline in about 35 per cent, codeine sulfate in about 30 per cent, atropine in about 25 per cent and theophylline-calcium salicylate in 23 per cent.

DR. PARDEE: What is meant by improvement, Dr. Gold?

DR. GOLD: In this case, he means an increase in the capacity to walk the "two-step" before pain appears. It is not a statement of how much increase, but what proportion of patients show some improved capacity.

I would like to ask Dr. Pardee if he would be willing to comment on this list of drugs for the control of angina of effort.

DR. PARDEE: What is the rest of that list?

DR. GOLD: It shows that 22 per cent of the patients improved with erythrol tetranitrate, 14 per cent with phenobarbital, 15 per cent with digitalis, 8 per cent with sodium nitrite and about 8 per cent with dinitrophenol. I might add that in the October 28, 1943, issue of the *New England Journal of Medicine*, Riseman classified potassium iodide in 1 Gm. enteric-coated tablets as markedly effective, and the same drug in similar doses in the form of a saturated solution as ineffectual.

DR. CHARLES H. WHEELER: Did they try a placebo?

DR. GOLD: Yes, they state they tried placebos and found that lactose did not bring about improvement by the "two-step" test. But when the patients' judgment of their state was used as a criterion, about 60 per cent of them stated that the lactose placebo made them better, and the figure for incidence of improvement was reduced to about 20 per cent in the case of lactose when a third criterion was used, namely, the number of attacks of pain in a period before and during the use of the placebo.

You see, they analyzed the improvement in three ways. One was in effect to ask the patient, "Do you think you were better or did the medicine help you?" The other was to ask, "How many attacks did you have?" The third was to have him exercise on the

"two-step" until there was pain. The three groups of answers did not match. They implied that the "two-step" test gave the most reliable results, and that the patients' own judgment of the value of the medicine was such an insensitive method that patients could not distinguish one drug from another, or as they put it: "The patient's estimation of therapeutic benefit indicated that all the drugs were approximately equal in value." Their chart, as you see, does not quite substantiate that statement; the incidence of improvement, according to the patients' evaluation, varied all the way from 25 per cent for nitroglycerin to 70 per cent for codeine. On the basis of the "two-step" test, the authors concluded that "one-half of the patients were benefitted by either aminophylline or quinidine sulfate," that codeine sulfate "rarely" enabled the patient to do more work before pain developed, and that atropine was "often of value." Again, these seem to be out of line with the data. They show about 40 per cent of patients were benefitted by quinidine, about 35 per cent by aminophylline, 26 per cent by codeine and 24 per cent by atropine. Are these differences significant? There is one of the defects in such studies from the scientific standpoint, namely, that they fail to determine the precision of the method. Since there are well known spontaneous variations in exercise tolerance in patients with coronary disease, and their own results show variations as wide as 100 per cent or more, it is necessary to determine how great they are, how frequently they occur, and how far off they throw such figures as we have quoted, which presume to show one drug more effective than another. If we read only the conclusions, the answers seem decisive; if we analyze the data carefully, we become very uncertain as to how matters stand.

Dr. Pardee, do you prescribe quinidine for the angina of effort?

DR. PARDEE: Since reading these reports, I have tried it. I have used quinidine in patients who did not seem to respond to anything else and so are the toughest patients on whom to try a new drug. I have not been impressed by its value.

DR. GOLD: Have you had any experience with that, Dr. Eggleston?

DR. EGGLESTON: No, virtually none.

DR. GOLD: Has anyone else?

DR. EGGLESTON: I never saw any logic in its use.

DR. PARDEE: Could we refer back to nitroglycerin for a moment? I do not understand the statement that patients are not improved by nitroglycerin. I think that must be dependent upon the definition of improvement.

DR. GOLD: Here was a group of about twenty patients in this report, who were given nitroglycerin to take at certain intervals during the week.

DR. PARDEE: How many times a day?

DR. GOLD: Some of them took it as frequently as every hour. At the end of this experience approximately 25 per cent of the patients judged the nitroglycerin to have helped them.

DR. PARDEE: I have used it that way at the suggestion of Roy Scott of Cleveland, who told me that he thought it was a very valuable method. It has not proved so in my experience.

DR. EGGLESTON: I, too, have employed it that way without conviction as to satisfactory results.

DR. GOLD: I know of patients with extremely frequent attacks of pain so that they were almost completely incapacitated, their pain recurring even at rest, in whom life became distinctly more tolerable with the dose of nitroglycerin under the tongue every hour.

In regard to the use of nitroglycerin I should like to stress the need for attention to dosage. I do not believe I have ever seen a patient requiring a dose to relieve the

heart pain, which is so large as to cause disturbing head symptoms. So many patients carry on with nitroglycerin in doses which nearly blow off their heads. They hesitate to take it frequently enough because of it. From the standpoint of relief of pain, they get on just as well when the dose is reduced below the threshold of head symptoms. I am also impressed with the need for urging patients to take nitroglycerin more rather than less frequently. They often fear habit or poisoning by it, and I am inclined to believe that physicians do not do enough to dispel those fears. There is no danger of either in proper therapeutic doses.

Dr. Eggleston, what do you do for the patient with coronary disease who is having attacks of pain at rest? How do you manage a person of that kind?

DR. EGGLESTON: This is the management of a patient with the decubital form of angina?

DR. GOLD: Yes.

DR. EGGLESTON: It has been my practice to attempt to find out whether there are any emotional, digestive or other factors which might have been responsible for precipitating these attacks of angina. If there are, I try to eliminate those as effectively as I can. Sometimes, sedatives in sizable doses will protect such a patient against decubital angina. Aside from that, the usual remedies are given in the hope that they will relieve the patient, and if they fail, then nitroglycerin. The value of nitroglycerin is to be judged in terms of the relief of the attack, and not in terms of continuous use during the day. It may also be used for the prevention of an attack. If the attack occurs at rather fixed intervals, the drug sometimes is very beneficial, and will tide these patients through. Usually there is some psychic disturbance in the form of dreams, or something similar to that which may or may not be unearthed on careful questioning of the patient, which seems to be responsible. I forgot to mention the rôle of the overdistended bladder. That occasionally seems to precipitate attacks. If the attacks then continue and are not relieved by the usual range of agents which you discussed here, many of which I do not use, I consider the desirability of a surgical approach for the relief of the angina, either by paravertebral block, which I do not particularly favor, or preferably by rhizotomy.

DR. GOLD: Is that what you do, Dr. Pardee?

DR. PARDEE: In patients with coronary pain at rest and at night, one might suspect a slow occlusion. We should examine the electrocardiogram and perhaps do a sedimentation test to rule out that factor. Having ruled that out, I approach it very much as Dr. Eggleston has outlined. In most of these patients, I think there is overactivity of the nervous mechanism causing spasm. Sedatives have been very successful in a number of cases. After large doses of phenobarbital, which keep them semi-stuporous for three or four days, they sometimes have much less pain when they come out of the depression. In a few cases this has marked the beginning of a conspicuous improvement. Nitroglycerin does not relieve most of these attacks. You ask them how long the attack lasted after the dose and they say "ten minutes." I think such a long period shows that the nitroglycerin was not responsible for the relief.

There is one drug, erythrol tetranitrate, which often helps the nocturnal attacks. A tablet of 30 to 60 mg. (½ to 1 gr.) seems to carry them through the better part of the night, and if they wake up in the middle of the night they can take a second one. I have not found mannitol hexanitrate as effective.

DR. GOLD: I should like to ask a question in relation to the large doses of sedatives. Do you ever find that large doses of sedatives make patients worse? They still awaken at

night with pain, and the pain is now much more severe. Before using the sedative, a mild pain would awaken the patient, and shortly after sitting up the pain subsided. Apparently, the pain in these cases is associated with the recumbent position. Under the influence of a large dose of a sedative, stronger stimulation is necessary to awaken them; and when they do awaken, the pain is excruciating. Such cases are not frequent but I have seen a few. It looks like intense sedation may be a double-edged sword.

Have you ever encountered that?

DR. PARDEE: No.

DR. EGGLESTON: I have not seen that.

DR. WHEELER: I think that surgery is the best bet for patients who are subject to severe attacks of cardiac pain at rest.

I should also like to mention that in patients with severe nocturnal pain and little or none during the day, hiatus hernia may be the cause. I have seen four or five such patients, and three of them had hiatus hernia.

DR. WALTER MODELL: I want to say that we had some experience with a few patients with just that type of symptomatology, who were relieved by the use of mercurial diurectics. I wonder if you could explain such a thing?

DR. EGGLESTON: I have seen a few of them benefitted by the mercurials.

DR. GOLD: I should like to stress the value of dehydration as a means of controlling cardiac pain which occurs at rest, and especially for those attacks which occur while the patient is resting in the recumbent position, nocturnal attacks of pain. Not all such patients respond, but some do in a dramatic way. I have the impression that the pain in those patients who also have exertional dyspnea or nocturnal dyspnea is more apt to respond well. Because of a clearcut relationship between the relief of the dyspnea and the pain by dehydration in some cases who have both symptoms, I am inclined to think that in some cases cardiac pain is the sole clinical manifestation of left heart failure. If you treat them as cases of left heart failure, their capacity for exertion without pain is enhanced and noctural pain may either lessen or vanish.

DR. EGGLESTON: Are not those the same patients in your experience who are benefitted by digitalis?

DR. GOLD: As a rule digitalis does not help them. Their symptoms improve when they lose several pounds of extracellular fluid, as the result of a milk diet which greatly restricts the salt intake, water ad lib, and a daily dose of a mercurial. Some of these patients are freed of nocturnal attacks of pain for two or three days after the dose of mercurial, and as the water is regained by the end of the week, the pain returns. A proper dosage regimen for maintenance has to be established. However, they have no manifestations of failure with congestion in the usual sense.

DR. EGGLESTON: Have you ever tried that without the mercurial?

DR. GOLD: I do not believe I have, but I should not be surprised, if satisfactory results were at times obtained without it, for salt restriction alone often brings about considerable dehydration.

DR. CATTELL: I think we would like to hear about the surgical treatment of coronary artery disease.

DR. BRONSON RAY: In general, there are three useful surgical procedures and these are all based on what we understand to be the anatomical arrangement of the innervation to and from the heart.

There are visceral afferent fibers from the heart, through the middle cardiac nerve to the middle cervical ganglion, through the inferior cardiac nerve to the inferior cervical ganglion, and by rami from the first to the fifth thoracic ganglia of the thoracic sympathetic chain. Visceral afferent fibers which transmit pain impulses are not called sym-

pathetic fibers. These afferent fibers pass through the ganglionated chain, and enter the cord via the posterior nerve roots. They have their cells of origin in the posterior ganglion, just as somatic afferent fibers do, and enter the cord to cross and ascend in the spinal thalamic tract. We believe that all pain impulses coming from the heart, regardless of what nerves they travel, enter the cord between the first and fifth thoracic segments. The innervation is, of course, bilateral.

Following the stimulus of the visit of Royal and Hunter to this country some years ago, stellate ganglionectomies were employed for a number of conditions, among them, anginal pain. In general, the operation included the inferior cervical and the first thoracic ganglia. In a number of patients this relieved the pain but in a greater number of others it failed. It was not until we began to try to formulate the anatomy of pain referred from the heart that the explanation was forthcoming. It is obvious that if, in a given case, the major portion of pain coming from the heart takes a course through nerves which traverse the stellate ganglion, the removal of that ganglion will stop the pain; but if some of the pain or all of the pain is mediated through other fibers, stellate ganglionectomy is a half-way measure or no measure at all.

The three procedures in vogue all consist of interrupting these afferent pathways either in the sympathetics or in the posterior roots. One procedure is the multiple injection of alcohol in the paravertebral region to destroy, by alcohol, the four or five upper ganglia of the thoracic ganglionated chain. Usually, the injection is made only into the first four, ignoring the fifth, because four needles are bad enough, and five are that much worse. To introduce a needle to the necessary depth (about 7 cm.) in the back is no mean procedure. It is a blind procedure at best and one must trust that his luck and skill together will get at least several of the needles near where he wants them. Then the alcohol is injected with the hope that it will destroy just the right nerves. Often enough, alcohol injection is successful in eliminating the pain but it has serious disadvantages which must be taken into consideration. These, I believe, can be listed as follows: There may be failure because it is a blind procedure. In a very high percentage, at least 30 per cent in my experience, there is painful radiculitis following this procedure as a consequence of alcohol acting on the intercostal nerves. This is not to be belittled because some patients who have been relieved of the angina would gladly exchange the one for the other after experiencing the radiculitis from alcohol. In one patient of mine radiculitis lasted for at least six months. I think his physician has never again considered an alcohol injection for such a case. Fortunately, however, other patients have had much happier results. That the alcohol or needle may enter the pleura causing pleurisy and even pneumonia is a recognized complication of the procedure. A more serious complication, and a few of these cases have been reported in the literature, is that the needle may somehow enter the subarachnoid space. The subarachnoid space comes out as a sheath along the nerve roots quite a distance sometimes. It is possible, when a needle is improperly placed, to inject alcohol into the subarachnoid space producing complete myelitis which has been permanent in some instances. There is the objection of recurrences of pain when the effects of the alcohol wear off. There is also the objection that, if the pain is bilateral or primarily substernal, the injections have to be made on both sides to be effective.

Another procedure is to resect the sympathetic chain, thereby interrupting the visceral afferent fibers going to the cord. At the same time, of course, the sympa-

thetic fibers are interrupted. A few years ago an article appeared in the *J. A. M. A.* in which the claim was made that this operation benefitted the circulation of the heart, because as the result of the removal of part of the sympathetic chain, dilatation of the coronary vessels could be expected. There was no proof for that, and such experimental information as we have would indicate that the reverse is probably true, that is, when the heart is sympathectomized, the coronary arteries appear to contract rather than to dilate. This is in contrast to what happens in the peripheral vasculatory system, in the hands, for example. So, whatever benefits accrue from the sympathectomy result from the interruption of afferent nerves carrying the pain.

The third operative procedure consists in cutting the first four or five posterior roots through a laminectomy. We are not sure how much of a rôle the fifth plays, and sometimes it is not convenient to cut more than four. We have had experience with this operation in eleven patients, with the sympathectomy in six patients, and I do not recall how many we have injected with alcohol, but the number is not large. I believe that there are certain advantages in the rhizotomy, the chief one being that, if the pain is bilateral, it is just as easy to cut the roots on both sides as on one, and thus a bilateral operation can be completed at one sitting. A sympathectomy on one side is just about as hazardous as a laminectomy and rhizotomy. I believe the choice of the operation needs to be suited to the case, and depends on whether the pain is unilateral or bilateral. There are also these points for consideration when deciding between the two operations. Horner's syndrome follows sympathectomy and is a disadvantage; it does not occur with rhizotomy. However, following rhizotomy there will be some sensory loss in the upper thoracic dermatomes, which is not serious, but nonetheless would be desirable to avoid if possible. There need be no demonstrable sensory loss after sympathetic resection.

Of the eleven patients with rhizotomy, one died on the second day postoperatively, of a recurrence of coronary occlusion. Another patient died three weeks after his operation when he was up and around the ward and presumably progressing satisfactorily. This was his first coronary occlusion. One patient was lost track of, but for the two months that we observed the patient after operation the result was satisfactory in that the pain was relieved and the patient felt gratified with the result. Two patients died two and three years, respectively, after operation. That leaves six patients that we now have under observation. One who was disabled for about ten years with his angina, following bilateral rhizotomy became head of a USO center in Connecticut. It is now nearly three years since his operation, but I am impelled to report that in the last six months he has again become incapacitated, has had what we believe to be a series of coronary occlusions, and has enough discomfort in his thoracic region to cause him a great deal of trouble.

Another patient who has been of great interest also, had angina for about eight years. He had a very unfortunate experience with an attempt at paravertebral block, and was miserable with neuritis from irritative effects of the alcohol. Both the neuritis and the angina were relieved by rhizotomy. This man, a physician, leads a life that would, I think, make almost any of us tired by midday. Another is a patient I do not feel very happy about. He is one of the clinic patients who was known to be a chronic complainer. Unfortunately, during the postoperative period of immobilization of the shoulder girdle he developed painful periarthritis and it, rather than the former angina, has become his chief source of discomfort. Therefore, the results, perhaps,

are not entirely satisfactory. The patients are not rehabilitated completely and there are disadvantages to almost any method. But from the standpoint of rational procedure in properly chosen cases I think that it has value.

There is reason to believe that there may be some other pathways for sensation from the heart. The patients who lose their pain by some operative procedure or other will get a warning of discomfort in the chest when they overexert themselves. It is nothing like their old pain, but it is a warning, and in two patients there has been the development after these operations of dull pain in the jaw region on both sides. The jaw pain does not come on nearly as frequently as the former angina pain did, and it is not disabling; it does not slow them up very much. The pathway or mechanism for that pain is a mystery.

DR. MODELL: Dr. Ray, in those patients who had coronary occlusion was there any pain during the attack?

DR. RAY: Yes, they had pain in the chest. It was different in degree and they recognized it as being somehow different in quality from any pain that they had had before.

DR. PARDEE: I remember one of those cases, a woman, who had coronary occlusion, and who died in the ward. In her final attack she had pain radiating from the right arm down to the hand.

DR. RAY: You might be interested in the review of the case of this girl who is being brought in on her bed. She is thirty-six years of age. She had angina for four years. Her mother and father both expired in the early fifties or thereabouts, with vascular disease, and one brother made a sudden exitus from coronary disease at the age of thirty-eight. Dr. Harold Stewart has examined this girl. Her pain occurred after exertion but it also often came at night and it also came when she was sitting still. Anxiety was rather the most consistent producer of her pain. The standard exercise tests left no room for doubting the diagnosis but she was thoroughly investigated for a possible diaphragmatic hernia. It is now five days postoperative; she had the sympathetics resected including the stellate and first five thoracic ganglia, and the chain in between. The left upper extremity shows all the effects of sympathectomy. It is warm and dry while the other is cool and moist. She also has a Horner's syndrome. She still has some discomfort in the operative wound, but she has had no angina to date, and she had not gone a day without it prior to the operation for four years even though she had spent some periods of time in bed.

How do you feel?

PATIENT: Fine!

DR. RAY: Do you think you would have had some pain by now?

PATIENT: I think I would have it right now in front of all these people.

DR. RAY: When she consulted me first she had two attacks in rapid succession. This is also interesting about her: She had not relied much on nitroglycerin because her attacks were short and the nitroglycerin gave her an uncomfortable feeling, particularly palpitation. She felt that taking the nitroglycerin really did not shorten the individual attack enough to warrant the discomfort of palpitation.

DR. GOLD: Was this a one-sided operation?

DR. RAY: The pain and the operation were left-sided. If pain had been bilateral I think I would have considered a bilateral rhizotomy through a laminectomy.

DR. GOLD: I think our time is up.

## SUMMARY

DR. GOLD: You will recall that in our first conference on this subject consideration was given to the general features of the treatment of the various clinical types of

coronary artery disease. There was some discussion of the treatment of shock with clyses, infusions of glucose and of plasma, the use of the xanthines like theobromine and sodium acetate, and aminophylline, and the use and dangers of digitalis in heart failure associated with coronary thrombosis.

The subject was extended today to include the question of bed rest in coronary thrombosis, morphine and the other opiates, sedatives, demerol, nitroglycerin, quinidine, papaverine, atropine, the mercurial diuretics and the surgical measures in the management of coronary artery disease.

Special attention was paid to the need for critical reading of the literature on the drugs used in coronary artery disease, and it was pointed out that the evidence for the value of most of them leaves much to be desired. The extraordinary spontaneous variations in the course of the susceptibility to pain in patients with coronary artery disease is a source of error in the judgment of the value of drugs, and this appears to be largely responsible for the differences in views regarding the value of drug therapy in this disease. Animal experiments are often misleading in that the results with massive doses may have no bearing on the use of these agents in the smaller therapeutic doses in man. Special attention was paid to the literature on atropine and papaverine. There seems to be considerable doubt regarding the utility of these agents in the dosage range which can be safely administered to man. Attention was called to the value of dehydration with salt restriction and the organic mercurials for the treatment of the patient subject to attacks of cardiac pain at rest or nocturnal attacks of pain. Several types of surgical procedures were described having as their purpose the interruption of the pain pathways from the heart, paravertebral alcohol injections, sympathectomy and rhizotomy.

# Clinico-pathological Conference

## Purpura, Arthritis, Hepatomegaly and Hepatic Failure*

STENOGRAPHIC reports, slightly edited,† of weekly clinico-pathological conferences, held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, B. T., a thirty-five year old dentist, entered the Barnes Hospital for the first time complaining of chills, fever and general malaise. The family history was significant in that the patient's father had diabetes and had had a stroke. Several members of his father's family died from the complications of hypertension. The past history revealed that at the age of ten the patient had an episode of jaundice. At eighteen he developed pneumonia and pleurisy, and following this illness, a diagnosis of pulmonary tuberculosis was considered and the patient was sent to Colorado for four months; he recovered completely. For some years the patient had attacks of acute pain in the upper abdomen which usually followed rich or fatty meals and lasted fifteen to twenty minutes. His stools had always tended to be loose, and six years prior to entry, at the time of an attack of abdominal pain, questionably tarry stools were noted. During the three successive summers preceding his first admission, the patient had attacks of malaria for which he took atabrine and quinine. One year before entry, he had mild cystitis which was apparently self-limited. He had never used alcohol to excess.

Two days prior to admission, the patient awakened with a chill, his temperature was found to be 102°F., and he complained of general malaise. The following day, although he had no more chills, the fever persisted, and he entered the Barnes Hospital on May 18, 1939.

On physical examination, the patient's temperature was 40°C., pulse 155, respirations 30, and blood pressure 120/88. He was moderately obese and appeared acutely ill. The pupils reacted normally. The sclerae were not icteric. The upper respiratory tract was normal and the lungs were clear. The heart was normal in size; the rhythm was regular, the rate rapid, and there were no murmurs. The liver edge was felt 8 cm. below the right costal margin. It was smooth, firm, slightly rounded and nontender. The spleen was not palpable.

The laboratory findings on entry were as follows: Blood count: red cells, 4,290,000; hemoglobin, 86 per cent; white cells, 7,200; differential count; "stab" forms, 29 per cent; segmented forms, 43 per cent; lymphocytes, 24 per cent; monocytes, 4 per cent. Blood smears revealed no malarial parasites. Urinalysis: negative. Blood culture: no growth. Kahn reaction: negative. Blood chemistry: sugar, 127 mg. per cent; nonprotein nitrogen, 22 mg. per cent. Agglutination tests: B. typhosus 4+, 1:80, 2+, 1:160, negative, 1:320; brucella, negative.

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Missouri.
† By Robert J. Glaser, M.D.

The patient was treated with quinine and his temperature became normal. A diagnosis of probable malaria was made and he was discharged on May 21, 1939.

After leaving the hospital, he continued to take quinine and felt well until one month before his second admission when he developed "boils." Although at one time he had as many as twenty, they all healed without treatment. One week later, he began to have pains in the knees, ankles, hips, elbows and wrists and some of the joints became swollen. The process was migratory but persistent, and the patient returned to the hospital for the second time on February 26, 1940.

The physical examination was unchanged except that there was slight swelling and tenderness of the ankles and wrists.

The laboratory studies revealed the blood count to be within normal limits. The corrected sedimentation rate was 1.5 mm. per minute. The blood sugar and non-protein nitrogen were normal. The blood cholesterol was 263 mg. per cent. An electrocardiogram was normal.

During his brief stay, the patient's temperature remained within normal limits. He was discharged on February 29, 1940, with a diagnosis of atrophic arthritis and hepatomegaly of unknown origin.

Following discharge, the patient's joint manifestations gradually subsided, and he was well enough to gain acceptance into the Army. After two years of service during which he worked hard, the patient again began to have intermittent episodes of swelling and pain in many of his joints, associated with purpuric spots on the lower legs. He entered an Army hospital where a diagnosis of infectious mononucleosis was made. While in the hospital the joint symptoms and purpura persisted. They recurred intermittently after he left the hospital and six months later, the patient re-entered an Army hospital for study. Liver function studies, done because of the hepatomegaly, were found to be normal. The gallbladder was not visualized on repeated cholecystograms. The patient was discharged without any diagnosis having been made.

The arthritis and purpura continued to occur intermittently. After an eleven-month interval, the patient was advised to re-enter the hospital for cholecystectomy although, at that time, he had no complaints referable to the biliary tract. At operation the gallbladder was found to be normal but the appendix, which was described as being acutely inflamed, was removed. A liver biopsy was reported as showing "hepatitis." Following the operation, the patient developed atelectasis of the left upper lobe of the lung, associated with cough and fever, which cleared in one week. Following discharge from the Army hospital, he continued to have arthritis and purpura of increasing severity. A high protein, high carbohydrate, high vitamin diet was given without apparent favorable effect. On two occasions the patient had sudden pain in the left upper anterior chest, associated with a non-productive cough and fever. Dyspnea on exertion gradually developed, as did ankle edema following moderate activity. One month before the third Barnes Hospital entry, slight bleeding from the nose, mouth and rectum was noted. Repeated examinations of the blood revealed the bleeding time, clotting time and prothrombin time to be normal, but the corrected sedimentation rate was persistently elevated. A low grade fever recurred periodically and the patient lost 30 pounds during the seven months following his discharge from the Army hospital. He returned to the Barnes Hospital for further study on December 11, 1945.

On entry the temperature was 36.8°c., pulse 100, respirations 16, and blood pressure 110/80. The patient appeared well developed and well nourished and was in no distress. Extensive purpura was noted on

both lower extremities, particularly over the legs and ankles where the lesions were confluent. The eye grounds were normal. Cervical and axillary nodes were soft and moderately enlarged. Examination of the upper respiratory tract was negative. The lungs were clear throughout and the heart was normal. Examination of the abdomen revealed a long, well healed scar in the right upper quadrant. The liver was felt 6 cm. below the right costal margin; the edge was quite firm, slightly tender and somewhat irregular. The spleen was not felt. There were questionable signs of ascites. The knees and ankles were painful on motion. There was no edema.

The laboratory findings were as follows: Blood count: red cells, 4,470,000; hemoglobin, 15.9 Gm.; white cells, 8,100; differential count, within normal limits; platelets, normal. Urinalysis: negative except for $4^+$ urobilin. Stool examination: negative. Quantitative Kahn reaction: 4 units. Blood chemistry: non-protein nitrogen, 11 mg. per cent; total proteins, 9.6 Gm. per cent; albumin, 2.3 Gm. per cent; globulin, 7.3 per cent. Icteric index: 30. Bromsulfalein test: 40 per cent dye retention in 30 minutes, 30 per cent in 40 minutes. Cephalin-cholesterol flocculation test: $4^+$. Hippuric acid test: 59 per cent excretion. Van den Bergh test: direct, 2.7 mg. per cent; indirect, 4.3 mg. per cent. D/I ratio: 62 per cent. Blood vitamin C level, 2.1 mg. per cent. Prothrombin time: 92.5 per cent of normal. Rumpel-Leede test: negative. Electrocardiogram: normal.

The purpura and joint pains persisted. The patient was placed on a diet devoid of milk, eggs and wheat; results were indifferent in that the cyclical character of the illness continued. Repeated Kahn tests were reported as doubtful. The patient developed increasing abdominal fluid. One month after admission, acute inflammation of the right eardrum was noted and penicillin therapy was instituted. The tympanic membrane was incised and purulent exudate was evacuated; on culture, alpha hemolytic streptococci were grown from the pus. An abdominal paracentesis was performed and 6,750 cc. of slightly cloudy, straw-colored fluid were removed. The specific gravity of the specimen was 1.006, and the total protein 1.4 mg. per cent. No tumor cells were identified on microscopic examination of sections of the centrifuged sediment. Following paracentesis the patient felt much improved, and at his own request, was allowed to return to his home. Slight nose bleeds and occasional melena were noted in the hospital, and low grade fever was present from time to time. At the time of discharge on February 15, 1946, the red cell count had fallen to 3,310,000 and the hemoglobin to 12.3 Gm. The icteric index was 30 and the total proteins 7.6 Gm. per cent. The patient was advised to follow a high protein, high carbohydrate, and low fat diet; vitamins, skimmed milk, and choline chloride were prescribed in large doses.

While at home, the patient developed a very good appetite, gained weight, and regained a feeling of well being. However, the reaccumulation of fluid in his abdomen again made him so uncomfortable that he was unable to eat and he re-entered the Barnes Hospital for the fourth and last time on February 22, 1946, for paracentesis.

The significant findings on physical examination included icterus, a markedly protuberant abdomen and purpura extending from the ankles to the thighs. No joint involvement was apparent.

The laboratory data were as follows: Blood count: red cells, 3,370,000; hemoglobin, 10.3 Gm.; white cells, 6,100; differential count, within normal limits; platelets, normal. Urinalysis: negative. Stool examination: guaiac positive. Blood chemistry: non-protein nitrogen, 16 mg. per cent; cephalin-cholesterol flocculation test, $4^+$;

total proteins, 7.1 Gm. per cent; albumin, 2.3 Gm. per cent; globulin, 4.8 Gm. per cent. Blood Wassermann reaction: positive.

A paracentesis was done and 3,250 cc. of slightly cloudy amber fluid, similar to that obtained on the previous admission, were removed from the abdomen. A Talma omentopexy had been advised by the physician who followed the patient at his home. At the patient's insistence, and despite the marked degree of liver damage, his request for operation was granted,and a laparotomy was performed; 500 cc. of straw-colored fluid were evacuated. The spleen was noted to be enlarged from two to three times its normal size. The stomach, duodenum and pancreas seemed normal. The size of the portal veins could not be determined because of adhesions from the previous laparotomy but the liver was small and nodular. The left lobe was biopsied, and omentopexy was performed. Microscopic examination of the biopsy specimen was reported as showing "portal cirrhosis."

Thirty-six hours after the operation, the patient complained of shortness of breath. His respirations gradually became slow, deep and irregular, and his pulse rate rose. The patient became increasingly drowsy, gradually lost consciousness and died quietly. During the last three days of life, his temperature, which had been normal, rose to 38°C.

## CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This is a very unusual case, presenting many interesting features. In discussing it, we can consider two separate aspects; first, the purpura and the associated arthritis, and second, the hepatic disease. Subsequently, they can perhaps be correlated. Dr. Reinhard, how would you classify the extensive purpura?

DR. EDWARD H. REINHARD: The results of the studies on the coagulation mechanism were normal. Therefore, I would explain the purpura on the basis of abnormal capillary permeability.

DR. ALEXANDER: Is not all purpura due to abnormal capillary permeability?

DR. REINHARD: In the sense that the blood must pass through the capillary wall, yes; often, however, the defect is primarily in the blood coagulation mechanism.

DR. ALEXANDER: Dr. Moore, if there is a defect in the blood coagulation mechanism, is there not also a defect in the capillary wall?

DR. CARL V. MOORE: Not necessarily. The classical example is in hemophilia, in which, although there is a defect in coagulation, purpura is extremely rare.

DR. ALEXANDER: The Rumpel-Leede test, which is usually positive in thrombocytopenic purpura, was negative here. Further, this man did not bruise easily. Are there any suggestions as to a diagnosis?

DR. REINHARD: There are certain features in this case which suggest a diagnosis of Henoch-Schönlein purpura. The joint manifestations and abdominal pain are both consistent.

DR. ALEXANDER: Is there anything against the diagnosis?

DR. REINHARD: I do not believe that all the findings are explicable on the basis of that diagnosis alone.

DR. ALEXANDER: If the hemorrhagic phenomena are considered apart from the evidences of liver disease, are they characteristic of Henoch-Schönlein purpura?

DR. MOORE: Yes, they are.

DR. ALEXANDER: The so-called triad which comprises Henoch-Schönlein purpura or Osler's purpura includes purpura or urticaria, arthritis and abdominal pain. These can occur singly or together. This patient's first hospital admission was for abdominal pain; he entered the hospital a second time with arthritis, and on his third admission he had both arthritis and purpura. In this syndrome the capillaries may

be permeable to plasma or blood; if the former, urticaria results, and if the latter, purpura. Indeed, hemorrhagic urticaria can be seen occasionally. Is there anything distinctive about the arthritis?

DR. REINHARD: It is cyclic and clears without residual; in these respects, it resembles the arthritis of rheumatic fever.

DR. ALEXANDER: Do you believe that the arthritis of Henoch-Schönlein purpura and that of rheumatic fever are indistinguishable?

DR. REINHARD: In rheumatic fever the joints are usually hot and red; in Henoch-Schönlein purpura they usually are not.

DR. ALEXANDER: Are there any other diseases in which arthritis, fever and purpura occur?

DR. W. BARRY WOOD, JR.: If urticaria is included, then serum sickness and drug allergies such as those seen with penicillin or the sulfonamides can be added.

DR. ROBERT J. GLASER: Meningococcemia also enters into the differential diagnosis.

DR. ALEXANDER: Yes. Rocky Mountain Spotted Fever as well as certain other infectious diseases must likewise be mentioned. Dr. Wade, this patient had a very high serum globulin. His total protein was 9.6 Gm. per cent with a globulin fraction of 7.3 Gm. per cent. What is your interpretation of these findings with respect to this case?

DR. LEO J. WADE: When the total proteins are increased, the increase is usually in the globulin fraction. Such increases in globulin can occur in such diseases as rheumatic fever, tuberculosis and pneumonia, but they are uncommon. More commonly, increases of this degree are seen in multiple myeloma, lymphopathia venerum, Boeck's sarcoid or lupus erythematosus.

DR. ALEXANDER: Arthralgia, fever and purpura are seen in lupus erythematosus not uncommonly. The skin lesions of lupus, in its later stages, can be purpuric. Is there any other disease in which fever, purpura, arthralgia and a high serum globulin are common?

DR. WOOD: They occur in periarteritis nodosa.

DR. ALEXANDER: That is correct. I would also add dermatomyositis. Some of the manifestations are reversible, particularly the arthritis, the purpura and the fever. In rheumatic fever, drug allergy, serum sickness and Henoch-Schönlein purpura, the patient almost always recovers from the initial attack. Attacks can occur repeatedly and yet leave no residual effects, except in the case of rheumatic fever in which irreparable heart damage is common. As to just when the changes become irreversible is a question of much interest to many investigators.

DR. WOOD: Dr. Alexander, do you believe that in this case microscopic lesions of periarteritis nodosa will be found?

DR. ALEXANDER: There is evidence that periarteritis nodosa may be the common irreversible lesion in severe rheumatic fever, serum sickness and certain forms of drug allergy. I know of no instance, however, of Henoch-Schönlein purpura in which periarteritis nodosa has been described; thus it is pure inference to say that because these other diseases eventually progress to irreversible changes, Henoch-Schönlein purpura may do likewise. As a matter of fact the number of cases of Henoch-Schönlein purpura that have come to autopsy is very small. For this reason the present case assumes great importance. I would not be surprised, however, if the lesions of periarteritis nodosa were found in this case.

This patient died of hepatic failure; his liver was noted to be enlarged on each physical examination from the time of the first admission in 1939 until his death. The only past history of significance in regard to the liver disease was that the patient had

had jaundice at the age of ten. It is very important that when he was observed in 1939, he gave a history of abdominal pain and tarry stools; from this information the inference is made that he had had purpura at that time. Dr. Wade, can the large liver and purpura be reconciled? If not, what was the cause of the hepatomegaly?

DR. WADE: In light of subsequent events, the hepatomegaly may have been merely a manifestation of an early stage of cirrhosis of the liver. I do not know of any way to relate the hepatomegaly and the purpura.

DR. ALEXANDER: As late as 1941 the patient was not very ill; he had no signs of liver disease and only the early signs of Henoch-Schönlein purpura. A biopsy specimen, taken in 1943 when the patient was in the Army, was reported as showing hepatitis. Coincidently, the purpura became more severe and the signs and symptoms of liver disease developed. That these changes were due to the same disease is not certain, but if not, the coincidence is striking. Dr. Wade has suggested that the signs first noted may have represented the early stages of cirrhosis. Dr. Wood, would you have any other interpretation?

DR. WOOD: I think Dr. Wade's suggestion is a good one. However, the patient had an attack of jaundice at the age of ten, and the question may be raised as to whether he did not have infectious hepatitis with repeated recurrences which eventually led to Laennec's cirrhosis of the liver. In favor of such a hypothesis is the report of the biopsy taken when the patient was in the Army.

DR. WADE: I would agree that infectious hepatitis may have been the cause of the cirrhosis.

DR. MOORE: Dr. Alexander, this patient may never have actually had malaria. His chills and fever may have been merely manifestations of recurring toxic hepatitis or infectious hepatitis—I do not know how these two could be differentiated.

DR. BRUCE KENAMORE: On the other hand, if the patient did have malaria, it may have contributed to the hepatic failure. It has been reported that chronic malaria causes liver damage.

DR. ALEXANDER: In relation to this discussion further comment should be made regarding the nature of the hepatic lesion. Both Dr. Moore and I saw slides of the specimen obtained on liver biopsy in 1943; it showed inflammation with much round cell infiltration about the liver cords, but there was, in our opinion, no evidence whatsoever of cirrhosis.

DR. ROBERT A. MOORE: The findings were not those of infectious hepatitis either.

DR. ALEXANDER: In 1943 the liver showed changes which were not those of either infectious hepatitis or cirrhosis; yet the patient died with some indications of portal obstruction which, therefore, must have developed within these two years. Dr. Wade, would relatively severe hepatitis cause such changes in a year's time? Would you expect to find a "hob-nail" liver in the final stage?

DR. WADE: From the surgeon's description at the time of the final laparotomy, it sounds as if the liver were cirrhotic. A finding which seems inconsistent with portal cirrhosis, however, is the total protein. Ordinarily, there is an increase in the globulin fraction in cirrhosis but it is a compensatory increase, and the total protein is not usually above normal. Unless the increased total protein is explained in some other way, the diagnosis of Laennec's cirrhosis seems somewhat doubtful.

DR. ALEXANDER: The high total proteins were noted only a few months before death, however.

DR. WADE: They assume less significance in that case.

DR. ALEXANDER: We must now decide whether the patient had hepatitis and pur-

pura as unrelated entities or whether conceivably the liver disease could have been a visceral manifestation of Henoch-Schönlein purpura. In view of the fact that in Henoch-Schönlein purpura the kidneys, the heart, and certainly the spleen may be effected, it is possible that the liver likewise might be involved.

DR. WOOD: Dr. Moore, would you comment further on your interpretation of the sections of the liver biopsy specimen.

DR. R. A. MOORE: I can only say that, in my opinion, this process represented a non-specific subacute hepatitis, and did not exhibit the pathologic picture of infectious or epidemic hepatitis.

DR. WOOD: Dr. Alexander, in view of the findings in the biopsy material I think the postulate that the liver disease was a manifestation of Henoch-Schönlein purpura should be entertained.

VISITING PHYSICIAN: Dr. Moore, were the blood vessels in the biopsy section abnormal in any way?

DR. R. A. MOORE: No.

DR. ALEXANDER: That is a good point. In Henoch-Schönlein purpura no structural lesion of the blood vessels is found. The permeability is increased without apparent structual damage. Are there any further comments?

DR. PALMER H. FUTCHER: Have either quinine or atabrine, which apparently this patient took on several occasions, been recorded as causing either liver disease or purpura?

DR. ALEXANDER: Dr. Moore, can you answer that question?

DR. C. V. MOORE: Not to my knowledge, but I am not thoroughly familiar with the literature.

DR. ALEXANDER: In summary, then, the concensus of opinion of this group seems to favor a single diagnosis, namely, Henoch-Schönlein purpura, to account for the purpuric, arthritic and hepatic aspects of the patient's disease. If this case is shown to be one of Henoch-Schönlein purpura with liver damage, it will be unique in the annals of medicine, for I believe that no such case is recorded in the literature. We shall ask the pathologists to give us the final answer.

Final Clinical Diagnosis: Henoch-Schönlein purpura.

PATHOLOGIC DISCUSSION

DR. ROBERT A. MOORE: The gross findings indicated first that there was some type of cirrhosis of the liver, but it was not of the usual type for there were large, irregular trabeculae throughout the liver in which the substance was entirely destroyed. In classical portal cirrhosis the nodules of regenerating liver cells are about the same size and are equally distributed throughout the liver substance. Second, there was splenomegaly, which had no particularly characteristic gross appearance, and there was two-fold evidence of portal hypertension; namely, ascites and ruptured varices of the esophagus with abundant evidence of hemorrhage. An unexplained polyserositis was indicated by pericardial adhesions and by adhesions involving the capsule of the liver and the transverse colon.

Turning to the microscopic sections, Figure 1 is representative of one part of the liver. There is total destruction of the liver with no structures remaining except the bile ducts; the connective tissue between the bile ducts is moderately cellular but not collagenous and it is heavily infiltrated with cells. Many of these cells are lymphocytes and mononuclear cells and a very few are polymorphonuclear leukocytes. Inspissated bile within the lumen of a bile duct may be seen. In the next section (Fig. 2), an area of regeneration is shown. There are large liver cells, many of them multinucleated, in association with the increased

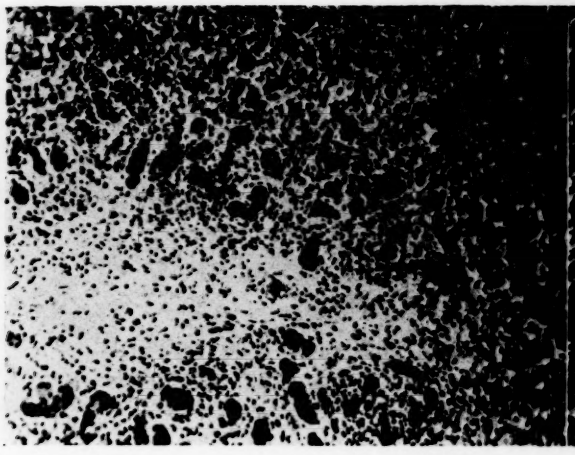


FIG. 1. Low power view of a section of the liver showing destruction of the parenchyma. Note the bile ducts with inspissated bile. x. 47.

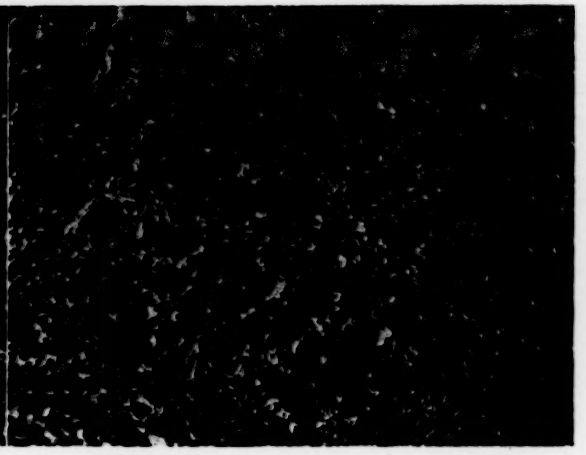


FIG. 2. Lower power view of a section of the liver showing areas of regeneration. Many of the liver cells are multinucleated and there is a heavy cellular infiltration. x 47.

fibrous tissue and the heavy mononuclear cellular infiltration seen in Figure 1. There was little evidence of actual necrosis of hepatic cells in any of the liver sections that we examined. The liver was regenerating; it had withstood the injury which was of

FIG. 3. Low power view of a section of the liver which shows essentially normal structure. Compare this section with those in Figures 1 and 2. x 47.

such a character that it had led to considerable cellular infiltration. In other words, this process resembled inflammation of the liver much more than cirrhosis of the liver; the latter I look upon as a degenerative rather than an inflammatory lesion with response chiefly on the part of connective tissue. Finally, in a third section taken at a distance from the others (Fig. 3), the liver appears entirely normal. The portal space contains the hepatic artery, portal veins, bile ducts and the surrounding hepatic cords arranged in a perfectly normal pattern. The Kupffer cells are a little more prominent throughout the entire liver than they should be, but they do not contain any pigment. There is no hemosiderosis.

Figure 4 is from the spleen and shows a central arteriole. There should be a surrounding follicle but none is present; instead there is "lymphocytic exhaustion" and the follicle is replaced by lymphocytes, many large mononuclear cells, and occasional heterotropic megakaryocytes—typical megakaryocytes were noted throughout the spleen. There are also nucleated red blood cells which indicate that the spleen was the site of extramedullary hematopoiesis.

In a section of bone marrow (Fig. 5), marked hyperplasia of megakaryocytes is seen. Large mononuclear cells such as were seen in the liver are present; these may be immature or degenerating megakaryocytes. The myeloid and erythroid elements in the bone marrow show a lack of maturation. There are very few well developed cells of either the red or the white series. Figure 6

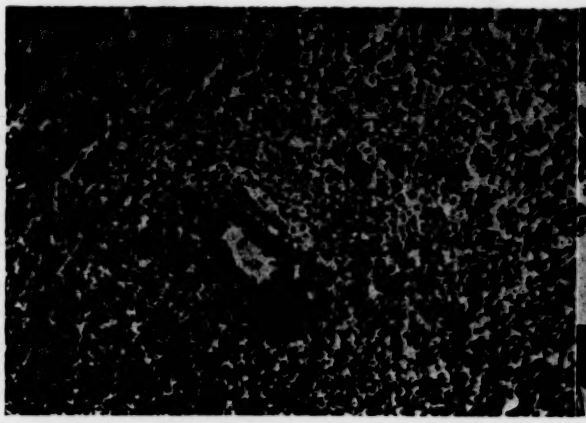


FIG. 4. Low power view of a section of the spleen. Note the absence of the normal structure about the arteriole. x 47.

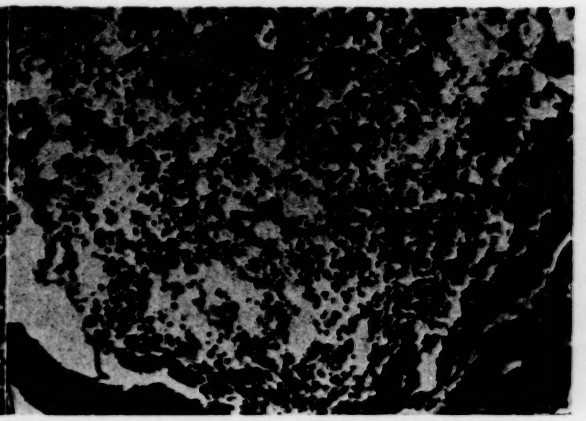


FIG. 5. Low power view of a section of bone marrow showing marked hyperplasia of the megakaryocytes. x 47.

is a higher power view to show these cells with a ragged outline and multiple, sometimes hyperchromatic nuclei. They are thought to be megakaryocytes. Degenerated, necrotic forms of these same cells are also seen. Occasionally, there are thrombi in the small capillaries of the bone marrow, liver and spleen. That the thrombi were present for a rather long time is evidenced by the foci of calcification in the bone marrow. These areas were apparently necrotic at first and subsequently became calcified.

To interpret the nature of the pathologic lesions in this case is extremely difficult. First, there was irregular destruction of the liver with almost complete loss of structure in some foci and none in others; there was also moderately active regeneration. Second, although limited focal deposits of hematin were noted in a few Kupffer cells, this finding may have been an artifact since there was no general hemosiderosis of the liver or the spleen. Third, there were exhaustion of the lymphoid tissue of the spleen and fibrosis of the splenic pulp. Although large mononuclear cells and multinucleated cells were present in the liver and the spleen, there was no evidence of a granulomatous process in any of the tissues. Extremely active erythrophagocytosis was seen in the spleen, many of the large mononuclear cells having been filled with partially digested red blood cells. Fourth, hyperplasia of the megakaryocytes in the bone marrow was prominent. There was suppression of maturation of cells of the red and white cells series; focal calcification, capillary thrombi, and cellular necrosis were found in the bone marrow. No living agent was demonstrated in these tissues.

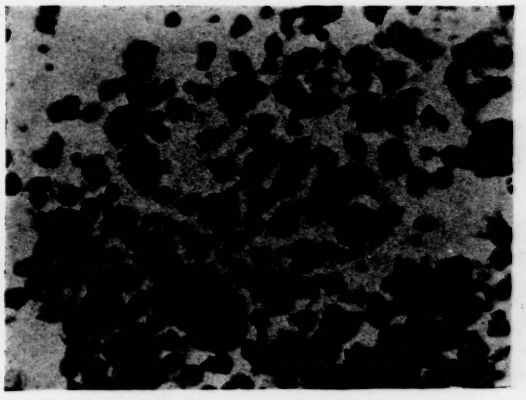


FIG. 6. High power view of the section seen in Figure 5. Note the large megakaryocytes, some of which are multinucleated. x 97.

In other words, this man had a disease causing enlargement of the liver of at least six years' duration, associated with purpura and arthritis for three years, eventually leading to portal hypertension and esophageal varices, and terminating in hepatic failure. During the same period of time he appar-

ently had malaria, an illness diagnosed as infectious mononucleosis, and after his first operation he had some form of pulmonary disease. The problem as I see it is to decide whether one diagnosis can account for all the major changes recorded in this patient's history since 1939; in other words, to answer the question that was asked in the clinical discussion: Was there a relation between the disease of the liver and the rest of the patient's illness, or did he have two or more diseases in sequence or together?

Malaria cannot be established in this case for the sections do not show any of the pathologic changes which are characteristic of chronic malaria. Infectious mononucleosis, if ever present, left no residuum. The disease which involved the joints was not destructive; when the knee joints were opened the articular cartilages were well preserved, and when the synovial tissue was examined microscopically, no evidence of inflammation was found. I would, therefore, feel reasonably safe in excluding rheumatoid arthritis. Likewise, no lesions suggestive of syphilis were present. If the patient had infectious mononucleosis and malaria, I think it must be assumed that they were intercurrent, unrelated diseases, although it is worthy of note that one case of supposed association of malaria and Henoch-Schönlein purpura has been reported in the Bulletin of the Veteran's Administration. It was the only case I could find. The pulmonary disease was probably an event of the patient's postoperative course—atelectasis, pulmonary embolus or bronchopneumonia. If the foregoing hypothesis is accepted, the purpura and the hepatic disease remain unexplained.

As far as I could determine going through the Quarterly Cumulative Index for the last fifteen years, there were only two titles which suggest that an autopsy had ever been performed on a patient with Henoch-Schönlein purpura, and both of the articles were in journals which were not available. I was, therefore, unable to find an adequate description of the pathologic anatomy of the disease. In going through all of the textbooks and monographs on the subject, the only information which could be obtained indicated that patients with Henoch-Schönlein purpura may have pericarditis, edema of the glottis and cerebral hemorrhage. It is stated that 20 per cent of them die of glomerulonephritis, but again I could not find any pathologic description or photomicrographs of kidneys from patients who had died with glomerulonephritis in association with this type of purpura.

I agree with the clinical diagnosis that this patient had Henoch-Schönlein purpura. If a significant number of patients develop an inflammatory disease of the kidney in association with Henoch-Schönlein purpura, why should not an occasional patient develop an inflammatory disease of the liver? In this case there was an inflammatory disease of the liver. It represented an example of so-called toxic or multilobular cirrhosis, or of a hepatitis, rather than an example of Laennec's cirrhosis. I believe, therefore, that in this patient the purpura on the one hand and the progressive, destructive hepatitis on the other were directly associated, and part of a single disease process.

DR. ALEXANDER: As you know, Sir William Osler was most interested in this disease and one might predict that a man of his scientific curiosity, confronted with a disease characterized variously by purpura, urticaria, erythema multiforme, abdominal pain, joint pains and nephritis would repeatedly refer to it throughout some twenty years of his medical career. He followed his cases carefully and in 1914 assembled all that was known about the disease at that time; and although he quoted a description of the pathologic findings in the kidneys of five patients who had Henoch-

Schönlein purpura, nowhere was there a complete autopsy report. I repeat, therefore, that this case takes on special significance indeed, for it clinically represented without doubt Henoch-Schönlein purpura and its associated lesions.

DR. WOOD: Dr. Moore, would you comment on the relationship between the thromboses in the liver in this case and those which Rich has described in sulfonamide nephroses.

DR. R. A. MOORE: The thromboses in this case were platelet and fibrin thrombi in capillaries not surrounded by any inflammatory reaction. I do not believe that they are related to the type observed by Rich. I would not put this patient's disease in the same category with lupus erythematosus or periarteritis nodosa.

DR. C. V. MOORE: Were you at all disturbed in your interpretation by the fact that in none of the diseases like lupus erythematosus or periarteritis nodosa, even though there may be considerable involvement of the liver, there is no associated cirrhosis?

DR. R. A. MOORE: No, since I do not look upon the changes in this case as those of ordinary cirrhosis; I consider the process here as a hepatitis and attribute the fibrosis to the fact that the disease went on for a number of years.

DR. C. V. MOORE: In lupus erythematosus or in periarteritis nodosa is fibrosis like this seen?

DR. R. A. MOORE: I have neither observed it nor have I seen it described. Glomerulonephritis is likewise uncommon; the lesion in the kidney in those diseases is distinct from that of glomerulonephritis.

*Final Anatomical Diagnosis:* Anatomic findings consistent with diagnosis of Henoch-Schönlein purpura; multilobular cirrhosis of liver; serosanguineous ascites (2000 cc.); generalized icterus, advanced; ruptured esophageal varices; altered blood in the stomach and intestines (2000 cc.); lymphoid exhaustion and fibrosis of spleen; erythrophagocytosis in spleen; hyperplasia of megakaryocytes in bone marrow; heterotopic megakaryocytes in liver and spleen; depression of maturation of myeloid and erythroid cells in bone marrow; recent hemorrhage in the superior and posterior mediastinum, abdominal wall, retroperitoneal space; hyperplasia of the tracheobronchial, periaortic, peripancreatic, periportal, and mesenteric lymph nodes; fibrous obliteration of the pericardium, partial.

# Case Reports

## Agranulocytosis Occurring after Exposure to a D.D.T. Pyrethrum Aerosol Bomb*

CLAUDE-STARR WRIGHT, M.D., CHARLES A. DOAN, M.D. *and* H. CAMPBELL HAYNIE, M.D.
COLUMBUS, OHIO

With the current release of surplus material by the War Department, the civilian markets have been flooded with various insecticidal preparations containing D.D.T. (dichlorodiphenyl trichloroethane). Since its introduction in Europe in 1939 and in America in 1942, the investigations relative to the toxic effect of D.D.T. on laboratory animals and man have been extensive. The consensus is that it is relatively safe,[4,20,21,33,22,37,32,23,24,29,26] however, recent reports indicate that it is not as innocuous as formerly thought.

The purpose of this report is to present a case of agranulocytosis which developed in a twenty-two year old, white male after exposure to the spray of a D.D.T. pyrethrum aerosol bomb. Evidence is presented which incriminates this preparation as the offending agent.

### CASE REPORT

A white, twenty-two year old man, a University student, came into the emergency room of University Hospital with the complaints of sore throat and tongue of twenty-four hours' duration with associated fever and chilliness.

Ten days before the onset of the presenting symptoms the patient had sprayed his apartment with an aerosol insecticide bomb which contained D.D.T., pyrethrum extract and difluorodichloro methane (Freon). During the interim between exposure to this insecticidal material and the onset of the symptoms the patient went about his usual school activities without appreciable difficulty. The day preceding his seeking medical attention he noted a small ulceration on the tip of the tongue. That evening he developed sensations of chilliness which persisted the next morning. The ulceration on the tongue progressed with generalized soreness of tongue and throat, which was accentuated when he attempted to eat. His temperature rose to 101°F. That afternoon, the second day of symptoms, he came into University Hospital.

On admission the temperature was 102.6°F. There was an ulceration 4 mm. in diameter with greyish membrane on the tip of the tongue. The oral pharynx was moderately hyperemic. The submandibular and angular lymph nodes were palpable and slightly tender.

The initial white blood count was 3,850 with the following differential: Neutrophiles 1 per cent, eosinophils 2 per cent, lymphocytes 75 per cent, monocytes 22 per cent. (Fig. 1.) Throat cultures were positive for Staphlococcus aureus and non-hemolytic streptococcus.

Penicillin, 30,000 units i.m. every three hours, was instituted. Local therapy to the oral lesions consisted of painting with ¼ per cent Gentian violet and warm Seiller's throat irrigations.

By the third hospital day the total white blood count had risen to 6,150, with 24 per cent neutrophils, 1 per cent basophils, 5 per cent eosinophils, 1 per cent myelocyte "C," 27 per cent small lymphocytes, 42 per cent monocytes, by the supravital technique. The red blood count was 4,910,000 with 14.6 Gm. of hemoglobin. The platelets were 898,160 per cu. mm. There was parallel improvement clinically with decline of the temperature to normal and healing of the oral lesions. The granulocytes gradu-

* From the Department of Medicine, College of Medicine, Ohio State University, Columbus, Ohio.

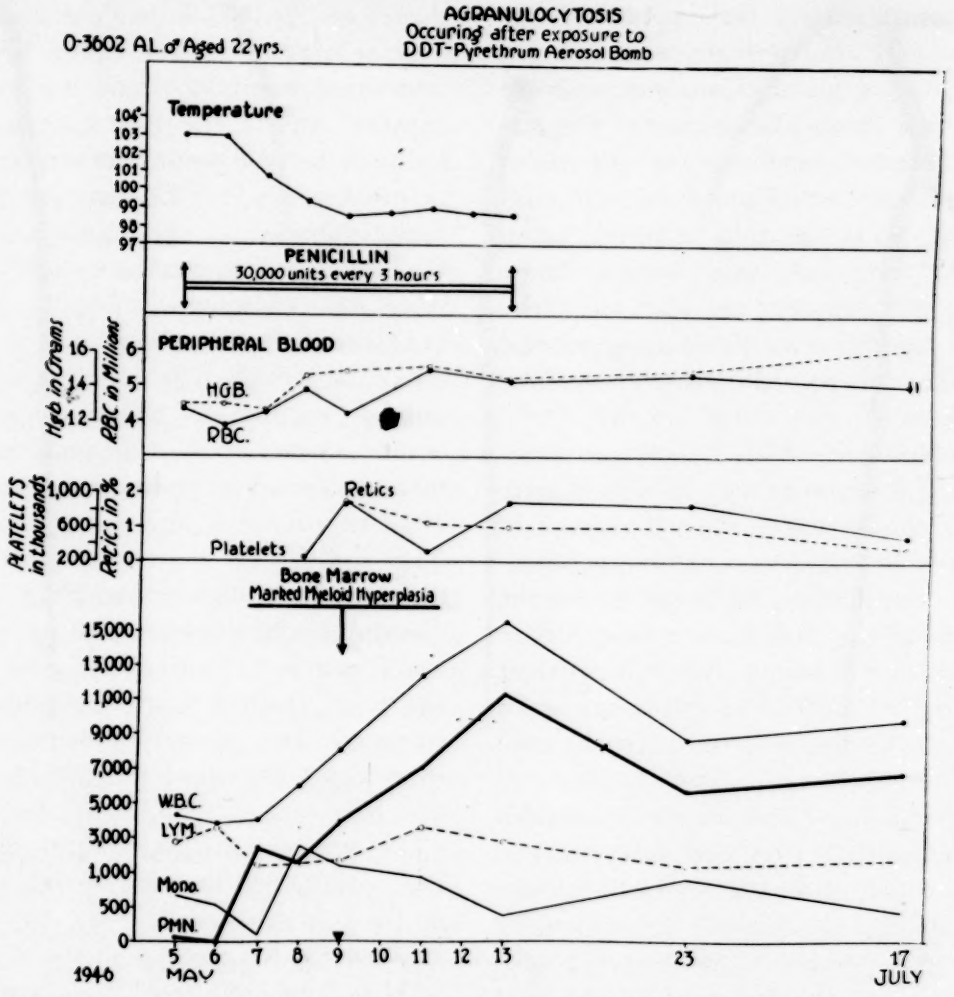



FIG. 1. The first hematologic studies were made eleven days after exposure to the aerosol bomb spray.

ally increased with a corresponding fall in the compensatory absolute monocytosis.

Examination of the sternal bone marrow, using the supravital technic, on the fifth hospital day showed a marked increase in the myeloid cell series, which were mainly at the "C" level. This hyperplasia was reflected in the overcompensatory peripheral blood findings four days later, at which time the white blood count was 15,600 with 73 per cent neutrophils.

Ten weeks after discharge the patient continued to remain clinically well and the hematologic studies at that time were as follows: total white blood count 9,600; with the following supravital differential; polymorphonuclear neutrophils 71 per cent, eosinophils 6 per cent, small lymphocytes 17 per cent, intermediate lymphocytes 1 per cent, monocytes 5 per cent. The red blood count was 5,090,000 with 16.3 Gm. of hemoglobin. The platelets were 498,820 per cubic mm.

## COMMENT

*Agranulocytosis.* The diagnosis of "ideopathic agranulocytosis" was very commonly made during the decade between the description of the syndrome by Schultz in 1922[27] and Kracke's[15,16] and Madison's and Squier's observations[17] that certain benzene ring compounds played a significant etiologic rôle. Now that many organic chemicals and metallic drugs have been demonstrated as potentially capable of causing profound depression of myelopoiesis in certain hypersusceptible individuals, a history of such

exposure must always be sought. In this case it was only after persistent questioning over several days that the history of exposure to the aerosol bomb was obtained. The patient then remembered using it with a cut on his hand and with some direct skin contamination. No medication had been taken during the preceding four weeks. There had been no exposure to any industrial chemicals, and no evidence of any bacterial or virus infection preceding the onset of the oral lesions.

In previous clinical studies of agranulocytosis in this laboratory, it was shown, through a correlation of bone marrow and peripheral blood observations, that approximately two weeks may be required for the maturation of the immature myeloblast to the mature, five-lobed, polymorphonuclear neutrophilic leukocyte.[9] In this instance the exposure to the spray of the aerosol bomb occurred ten days preceding the onset of clinical symptoms. The insult to myelopoiesis undoubtedly occurred then, but was not reflected symptomatically until the delayed peripheral neutropenia developed. By the time the peripheral neutropenia was manifested through the onset of the oral lesions, chilling and fever, a compensatory monocytosis plus regeneration of the myeloid elements was already occurring; followed, after a brief latent period, by beginning regression of the clinical syndrome. The bone marrow fifteen days after the original exposure and five days after appearance of symptoms revealed the myeloid elements in a stage of rebound hyperplasia, even though there was still a moderate peripheral neutropenia (24 per cent). This bone marrow recovery with hyperplasia was only fully reflected in the peripheral blood several days later. (Fig. 1.)

The D.D.T.-pyrethrum mixture is much more effective as an insecticide than either chemical used alone. The pyrethrum acts as a contact insecticide, thus allowing the slower acting D.D.T. to exert its effect as a central nervous system toxin. The aerosol insecticide bomb to which this patient was exposed was of the type that was manufactured for the armed forces under specifications of the War Department. The small metal cylinder, 6 cm. long, contained 10 Gm. net contents. On the carton was stated, "Aerosol Insecticide Bomb containing D.D.T. and Pyrethrum extract . . . Ingredients active 16½%, inactive (difluorodichloro methane) 83½% . . . Caution: avoid contact with skin and don't spray on food. Avoid excessive breathing of spray. If taken internally, use emetic of mustard." The metal pin in the open end of the cylinder is broken off to release a spray cloud of about six seconds' duration. Warning is made to hold spray away from the operator. Inquiry from the manufacturers revealed that in addition to the above ingredients the bomb contained sesame oil and lubricating oil (SAE 30).*

Thus, any of the ingredients—the D.D.T., the pyrethrum, the sesame oil, the Freon, or the lubricating oil, (SAE 30)—could be indicated as the noxious agent. Neal[25] states, "There is no definite evidence which should indicate that D.D.T. produces any marked or characteristic change on the blood cell picture. Studies of the blood constituents during chronic subacute D.D.T. poisoning in dogs reveal only a drop in hemoglobin, which over a period of days results in hypochromic anemia. It is considered that this anemia is related indirectly to the dietary deficiencies produced by prolonged anorexia and inadequate food intake during repeated periods of tremors and convulsions." Similar observations have been made by Telford.[31] Acute D.D.T. toxicity has been characterized predominantly by central nervous system irritability—nervousness, tremors and generalized convulsions. In chronic toxicity in animals two path-

* Manufactured by Kidde Manufacturing Co., Inc.

ological lesions, centrolobular necrosis of the liver, and, less frequently, focal necrosis of striated muscles, have been most commonly observed.[2]

Three deaths have been cited in England. In two instances D.D.T. preparations were taken with the intent of suicide. In one, 6 ounces of 20 per cent D.D.T. in cyclohexanone was taken and in the other an unknown amount of 6 per cent D.D.T. in kerosene. In both death was attributed to the solvent.[2] In the third case 1 ounce of 5 per cent D.D.T. in kerosene was ingested by a one and one-half year old child resulting in death within four hours.[11]

Case[5] and Hill and Robinson[11] have shown in their studies in both man and animals that either direct skin contact or ingestion of mixtures of D.D.T. in oil can produce significant toxic effects. In a carefully controlled series of observations carried out on two normal human subjects in an experimental chamber, Case noted among other changes a granulocytopenia (6,900 to 1,412 and 6,528 to 1,512), which developed in both men on the third to fourth days following a forty-eight-hour exposure to a D.D.T.-oil mixture. There was a delayed absolute lymphocytosis up to 5,170 and 5,208 per cubic mm. on the nineteenth and forty-ninth days, respectively. From the clinical and experimental data presented by these investigators it appears that the toxicity of D.D.T. may be enhanced by mixing with certain oil solvents, and that among other organs the bone marrow may be affected. Case presents the first and only positive evidence to date suggesting the value of careful hematologic studies in the early recognition of D.D.T. intoxication.

Pyrethrum, a powdered insecticide obtained from the flower-heads of members of the chrysanthemum family, has been noted by Chevalier[6] to be toxic to warm-blooded animals only when administered intravenously in large doses. It has also caused mental confusion in those exposed to long periods of heavy concentrations. No evidence has been reported suggesting any noxious effects on the blood elements.

Difluorodichloro methane (Freon) is commonly used as a refrigerant. Kehoe[13] states that levels as high as 20 per cent in air have caused no apparent deleterious effect in animals. Humans have experienced exposure to concentrations of 8 to 12 per cent without appreciable harm. There have been recently noted three instances in which serious burns to the hands resulted from improper use of the aerosol bomb.[14,19] In all instances, the hand was placed over the suddenly released pyrethrum—D.D.T.—Freon spray cloud. The Freon caused immediate freezing of the fingers or hands which resulted in third degree burns. In one case the two distal phalanges of an index finger were sacrificed.

Sesame oil is a frequently used solvent for pharmaceutical purposes, particularly in hormone therapy and no deleterious effects have been ascribed thus far to it.[36]

*Therapy.* A number of recent reports have cited the efficacy of the newer forms of antibiotic therapy in tiding over the acute phase of a toxic agranulocytosis until the bone marrow can recover spontaneously.[1,12,30,-18,7,28,10,34,3,35] This case is another to be added to the list of therapeutic successes. However, it should be emphasized that this *antibiotic reprieve* is effective only if the insult is of a mild and temporary nature. If the damage to the bone marrow is so potent and massive that myelopoiesis is more than transiently impeded or destroyed, this temporary suppression of secondary bacterial invaders does not guarantee permanent recovery.

Two such instances of failure have been seen recently in this clinic. The first was a thirty-four year old white woman (G.K.-0.7642) who had taken five to six "B. C. Headache Powders" (acetanilid) daily for

the past year. When she was first seen she had only 700 circulating white blood cells, with no granulocytes in the differential count. Examination of a specimen of sternal bone marrow with the supravital technic revealed only 0.5 per cent myeloid elements. There was a generalized pan-marrow hypoplasia. Blood cultures were positive on four occasions for Klebsiella pneumoniae, in spite of intensive sulfadiazine (6 Gm. daily) and penicillin (400,000 units daily) therapy. Streptomycin therapy (totaling 9,500,000 units) was begun five days before death. Blood cultures became negative on the third day and remained sterile the last two days of life, although the bone marrow and peripheral blood pictures failed to respond. Autopsy findings were consistent with the clinical diagnosis and observations.

In the second instance a forty-one year old white woman (E.U.-0.7325) developed severe angina with agranulocytosis (white blood count 200) after a two-weeks' course of thiouracil (0.2 Gm. daily) for hyperthyroidism. Six months previously she had taken 16.8 Gm. of thiouracil over a six weeks' period for the same symptoms, at the conclusion of which she had an episode of "acute tonsillitis and fever" of questionable etiology and without blood cell data having been obtained. From the subsequent course of events it may be assumed that the myeloid elements of the bone marrow had been sensitized by the first course of thiouracil, and when the second course was instituted, of considerably smaller dosage, the injury to these elements was disproportionately great and severe. The red blood cells and platelets remained within normal limits. The overwhelming infection after twenty-four hours of intensive penicillin therapy showed no progression and slight clinical improvement. The patient expired suddenly, however, at the end of this brief hospitalization, after two generalized convulsions. At postmortem the brain showed bleeding into Virchow-Robin's spaces with focal bleeding in the brain substance and subarachnoid space. There was marked universal toxic hypoplasia of all bone marrow.

## CONCLUSIONS

1. A case of agranulocytosis occurring after exposure to an aerosol insecticide bomb is presented. The bomb contained D.D.T., pyrethrum, sesame oil, petroleum oil (SAE 30) and difluorodichloro methane (Freon). The known toxic effects of these ingredients are discussed briefly. The time interval of the onset of symptoms after exposure, the inability to discover contact with any other known myelotoxin, the lack of any signs of an acute infection before the onset of oral lesions, along with the recent experimental evidence that D.D.T. in oil may cause a granulocytopenia in man,[5] are factors incriminating this preparation as the toxic agent.

2. At least three instances of severe burns to the hands and fingers resulting from the misuse of aerosol bombs have been observed. These were due to the difluorodichloro methane (Freon).

3. The value of antibiotic therapy as a temporary emergency inhibitor of secondary bacterial invaders during the period of transient agranulocytosis is emphasized and illustrated in the case presented. In addition to the limitations of specific bacteriologic susceptibility, antibiotics are effective at best only when the toxic depression is very transitory and the bone marrow's recuperative powers are permitted to assert themselves promptly after the insult. Two instances of fatal agranulocytosis, one due to prolonged administration of acetanilid and another to sensitivity developing during thiouracil therapy are noted as examples of failure with antibiotic and all other adjuvant therapy.

4. Evidence is beginning to accumulate

which indicates that D.D.T.-oil mixtures are potential toxins to bone marrow as well as to other organs. With the widespread and indiscriminate use of these preparations at the present time, the granulocytopenic syndrome probably will be observed more frequently. Careful hematologic studies in those working in heavy or repeated exposure are indicated to detect early toxic effects and to prevent irreversible bone marrow damage.

## REFERENCES


1. Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., Jennings, M. A. and Florey, H. W. Further observations on penicillin. *Lancet*, 2: 177, 1941.
2. Biology Subcommittee—National Research Council, Insect Control Committee, Minutes of Conference on Toxicity of D.D.T. to Man and Other Mammals and the Hazards Involved in the Agricultural Use of D.D.T. May 24, 1946, Washington, D. C.
3. Boland, Edward W., Headley, Nathan E. and Hench, Philip. The treatment of agranulocytosis with penicillin. *J. A. M. A.*, 130: 556, 1946.
4. Cameron, G. R. and Burgess, F. The toxicity of 2, 2-bis (p-chlorophenyl) 1,1,1-trichlorethane) D.D.T. *Brit. M. J.*, 4407: 865, 1945.
5. Case, R. A. M. Toxic effects of D.D.T. in man. *Brit. M. J.*, 2: 842, 1945.
6. Chevalier, J. Cited by Wood and Osol.[36]
7. Dameshek, William. Leukopenia and Agranulocytosis. New York, 1944. Oxford University Press.
8. Dameshek, William and Knowlton, H. C. The use of penicillin in the treatment of sulfonamide agranulocytosis. *Bull. New England M. Center*, 7: 142–148, 1945.
9. Doan, Charles A. The neutropenic state. *J. A. M. A.*, 99: 194, 1932.
10. Harford, C. G., Martin, S. P., Hageman, P. O. and Wood, W. B., Jr. Treatment of staphylococcic, pneumococcic, gonococcic and other infections with penicillin. *J. A. M. A.*, 127: 325, 1945.
11. Hill, K. R. and Robinson, G. A fatal case of D.D.T. poisoning in a child. *Brit. M. J.*, 2: 845, 1945.
12. Keefer, C. S., Blake, F. G., Marshall, E. K., Lockwood, J. S. and Wood, W. B., Jr. Penicillin in the treatment of infections. *J. A. M. A.*, 122: 1217, 1943.
13. Kehoe, Robert. Personal communication.
14. Kelly, E. G. Personal communication.
15. Kracke, R. R. Recurrent agranulocytosis; report of an unusual case. *Am. J. Clin. Path.*, 1: 385, 1931.
16. Kracke, R. R. and Parker, F. P. The etiology of granulopenia (agranulocytosis) with particular reference to drugs containing the benzene ring. *J. Lab. & Clin. Med.*, 14: 799, 1934; *Am. J. Clin. Path.*, 4: 453, 1934; The relationship of drug therapy to agranulocytosis. *J. A. M. A.*, 105: 960, 1935.
17. Madison, F. W. and Squier, T. L. The etiology of primary granulocytopenia (agranulocytic angina). *J. A. M. A.*, 102: 755, 1934.
18. Meredith, W. C., Douglas, A. H. R. and Fink, Harold. Penicillin in malignant granulocytopenia. *U. S. Nav. M. Bull.*, 43: 1017, 1944.
19. Metzler, Dwight F. Injury resulting from use of aerosol bomb. *Public Health Rep.*, 61: 15, 1946.
20. Neal, P. A., von Oettingen, W. F., Smith, W. W., Malmo, R. B., Dunn, R. C., Moran, H. E., Sweeney, T. R., Armstrong, D. W. and White, W. C. Toxicity and potential dangers of aerosols, mists, and dusting powders containing D.D.T. Supplement No. 177 to the Public Health Reports, 1944.
21. Neal, Paul A. A report on the toxicity to warm-blooded animals of aerosols, mists and dusting powders containing D.D.T. *Soap & Sanitary Chemicals*, 21: 99, 1945.
22. Neal, P. A., von Oettingen, W. F., Dunn, R. C. and Sharpless, N. E. Toxicity and potential dangers of aerosols and residues from such aerosols containing three per cent D.D.T. Supplement No. 183 to the Public Health Reports, 1945.
23. Neal, Paul A., and von Oettinger, W. F. The toxicity and potential dangers of D.D.T. to humans and warm-blooded animals. *Med. Ann. District of Columbia*, 15: 15, 1946.
24. Neal, P. A., Sweeney, T. R., Spicer, S. S and von Oettingen, W. F. The excretion of D.D.T. (2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane) in man, together with clinical observations. *Public Health Rep.*, 61: 403, 1946.
25. Neal, Paul A. Personal communication.
26. Queries and Minor Notes: D.D.T. Poisoning. *J. A. M. A.*, 130: 56, 1946.
27. Schultz, Werner. Ueber eigenartige Halserkrankungen: (a) Monozytenangina (b) Gangranezierende Prozesse und Defekt des Granulozytensystems. *Deutsch. med. Wchnschr.*, 48: 1495, 1922.
28. Smith, L. B., Cohen, Frank and Nichols, R. G. Agranulocytosis treated with penicillin. *J. A. M. A.*, 126: 1027, 1944.
29. Smith, M. I. Accidental ingestion of D.D.T., with a note on its metabolism in man. *J. A. M. A.*, 131: 519, 1946.
30. Sprague, H. B. and Ferguson, L. K. Agranulocytosis treated with penicillin. *U. S. Nav. M. Bull.*, 43: 1014, 1944.
31. Telford, Horace, S. Personal communication.
32. Telford, Horace, S. D.D.T. Toxicity. *Soap & Sanitary Chemicals*, 21: 161, 1945.
33. Tolerance Figure Suggested for D.D.T., AIF News, P. 3, (Jan.–Feb.) 1945.
34. Tyson, Mary Catherine, Vogel, Peter and Rosenthal, Nathan. The value of penicillin in the treatment of agranulocytosis caused by thiouracil. *Blood*, 1: 53, 1946.
35. Urbach, Erich and Goldburgh, Harold L. Agranulocytosis induced by aminopyrine suppositories. *J. A. M. A.*, 131: 893, 1946.
36. Wood, H. C. and Osol, Arthur. The Dispensatory of the United States of America. 23rd ed., Philadelphia, 1943. J. B. Lippincott Co.
37. Woodward, G., Ofner, R. R. and Montgomery, C. M. Accumulation of D.D.T. in the body fat and its appearance in the milk of dogs. *Science*, 102: 177, 1945.

# Lupus Erythematosus Disseminatus in a Male*

CAPT. W. CLAY DINE *and* LIEUT. COL. C. STUART WILSON
MEDICAL CORPS, ARMY OF THE UNITED STATES

A CASE of disseminated lupus is reported as to its symptoms, clinical course and the pathological changes as seen at postmortem.

## CASE REPORT

A white male, age twenty, entered military service in January, 1943. His habits were excellent. Father and mother were living and well. He was the only child. The only allergy history was that the maternal grandfather had asthma. He had had mumps, measles and chickenpox in childhood without complications. Tonsillectomy and adenoidectomy were performed in 1932.

In November, 1943, nine months after entering the service, he noted that he had pains in his ankles and knees after hikes which would persist for a couple of days. The following month, December, he noticed some tiny, red, elevated lesions on both forearms. These gradually increased in size and after about two months receded.

He first reported on Sick Call on February 5, 1944, while in England, with chills, high fever, vomiting, and tender painful joints, generalized ecchymotic rash over the extremities, petechiae on trunk, and generalized lymphadenopathy. Meningococcemia was suspected but his spinal fluid and blood culture were negative. He was treated with sulfonamides. The rash faded and disappeared within a week. Fever of between 100° and 101°F. persisted. Two weeks later he developed fever (104°F.), chills, and an erythematous type of rash appeared, distributed over the entire body. The diagnosis of "erythema multiforme" was made. This acute phase was followed by a two-week period during which he ran a low-grade fever, rapid pulse, low white count (below 4,500), and slightly elevated sedimentation rate. Five weeks after the acute onset he suddenly developed sharp pain in the anterior chest with a pericardial friction rub associated with a soft, blowing, systolic murmur at the apex. After six days a pleural friction rub was detected over the left lower chest. Electrocardiograms did not support a diagnosis of pericardial effusion. *X*-rays of the chest showed an increased density over left lower chest. These symptoms subsided and during the last two weeks in March and all of April the patient felt well except for occasional joint pains and slight elevation of temperature.

He was evacuated to the United States and admitted to Billings General Hospital on May 16, 1944, with a transfer diagnosis of: "Acute rheumatic fever with erythema multiforme, acute pericarditis, and left pleural effusion." On the boat he had gone on deck to get some sun and had noticed that the previous quiescent lesions on his forearms had become bright red.

Physical examination revealed the following: Weight 140 pounds, height 72 inches, temperature 98.6°F., respirations 22, and blood pressure 115/72. There was a brownish discoloration over the bridge of the nose and also over the upper chest (this was more prominent when examined in a not too bright light). On each forearm were small scaly patches sharply defined with bright redlined borders. On the left buccal surface there was a sharply defined flat, shallow ulcer with white streaked center and red border which was painful. The submaxillary and cervical glands were enlarged but not tender. There was a limitation of excursion of the left lower chest but no physical signs of fluid. The heart was normal in size, shape, position and sounds. The abdomen was negative and lower

* From the Medical Service, Billings General Hospital, Fort Benjamin Harrison, Indiana.

extremities revealed no changes. The shoulders, elbows and hands were painful but presented no swelling or redness. Urine was normal chemically and also the sediment; red blood count 4,600,000; white blood count 5,000 with normal differential. Sedimentation rate was 20 mm. in one hour; total protein 7.2 A.G. ratio normal. Chest *x*-ray was reported as showing normal lung parenchyma, some calcified nodes in right hilum, and heart shadow normal.

During his first two weeks at this hospital he ran very slight elevation of temperature, ate well, gained weight and generally felt he was improving. On August 8th, he developed transient edema of both eyelids followed by painful herpetiform lesions on his buccal surfaces. One week later he complained of pain in his left arm and two somewhat hard nodules appeared on the extensor surface of the left arm. On palpation these were slightly elevated, indurated, and tender. They were reddish in color and persisted for three days. A muscle biopsy done at this time was reported as showing diffuse angiitis of periarteritis nodosum type. Early in August, signs of pleural exudation appeared in the left chest; i.e., limited expansion, absence of breath sounds, percussion impairment and diminished fremitus. Thoracentesis confirmed these clinical findings and from August 8th to November 30, 1944, nine chest taps were done with an average of 1,500 cc. for each aspiration.

There was nothing unusual in the pleural fluid and animal inoculation was negative. During the period of August through November, the heart rate was more rapid. A systolic murmur was heard over the apex and into the axilla; a gallop rhythm appeared. There was a period when the heart sounds became inaudible and cardiac dullness seemed much increased and a pericardial effusion was suspected. The heart sounds reappeared without aspiration. During December, 1944, the joints again became very tender; cervical and epitrochlear lymph nodes became palpable. A node was removed for biopsy which was reported as reactive lymph node with marked hyperplasia. "While the lymph node is purely one of non-specific reactive nature and each of the microscopic cellular vascular and collagen changes alone might have little significance, the sum of all the minutiae even though necrosis is not present would be consistent with a diagnosis of Dermatomyositis or Lupus Erythematosus Disseminatus" (William Antopol, Major, AUS, Chief of Laboratory Service).

A purulent discharge appeared from the left ear, was diagnosed otitis media, which promptly responded to penicillin therapy. A gradual reduction in red cells and hemoglobin was observed. During the following month he showed general improvement and this remission lasted about thirty days.

The next relapse was ushered in by a recurrence of the herpetiform painful ulcers in his mouth and throat. Purulent sputum appeared, fever was higher, pulse fast, the patient had headache, felt weak, and for the first time edema of his extremities and fluid in the abdomen were present. The urine, for the first time, in February 1945 showed evidences of renal involvement by the presence of albumin, red cells, and casts. The red blood count was 3,200,000; hemoglobin 71 per cent; white blood count 4,500; sedimentation rate 30 mm. for one hour; total proteins 7.3 per cent; albumin 3 per cent; globulin 4.3 per cent; non-protein nitrogen 36 mg. per cent; urea 14 mg. per cent; cholesterol 100 mg. per cent.

During March his sedimentation rate rose to 60 mm. per hour; red blood count was 2,700,000; hemoglobin 56 per cent; total proteins 5.6 per cent with albumin 1.6 per cent; and globulin 4 per cent. Transfusions of whole blood and also plasma failed to divert the downward course and the patient died March 23, 1945, seventeen months after onset.

## COMMENTS ON CLINICAL COURSE

*Fever.* At the onset the temperature remained elevated for twenty-seven days except for four mornings when the reading was either normal or subnormal. This period was followed by two months of normal temperature range except for two consecutive days of elevation. This was followed by ten weeks of continuous fever. During the following month the temperature was again normal. During the rest of

his illness he ran fever with the exception of five periods of approximately ten days each. There were seven remissions of variable length, judging by the temperature curve.

Curiously enough, during the period of early pericardial and pleural involvement, he had only five days of fever followed by two months of normal temperature. Early in August and through November, 1944, he was having pleural exudation with frequent aspirations and three of the ten-day fever free periods occurred during these months. (Fig. 1.)

*Skin Manifestations.* In December, 1943, small, red, elevated lesions appeared on both forearms. On February 6, 1944, at time of onset, a petechial rash appeared over trunk with ecchymosis over lower extremities. On February 21st, after two weeks of sulfadiazine medication, a diffuse erythematous rash appeared with painless buccal ulcers. At the time this was considered a drug rash. On March 4, 1944, a dry scaly flush appeared over the face and was attributed to tear gas to which the patient had been exposed. On May 16th, a definite butterfly lesion over the nose and malar surfaces was observed. There were sore, painful, buccal lesions present. On each forearm were scaly patches with bright red borders. On August 18th, painful herpetiform buccal ulcers reappeared. Two painful nodules appeared on left forearm. On February 3, 1945, painful herpetiform buccal ulcers recurred.

*Joints and Muscles.* No marked joint swelling or redness appeared but during most of the course of the disease joint and muscle tenderness was a prominent symptom.

*Laboratory Studies.* The blood showed a persistent tendency toward leukopenia with occasional rises, associated with secondary changes such as sore throat, colds, or bronchial purulent material. The red cells showed a very slowly developing anemia with anisocytosis, poikilocytosis and hypochromia. The sedimentation rate in one hour varied from 15 mm. to 30 mm. throughout, except terminally when it rose to 62 and 70 mm. per hour. Blood cultures were all negative.

*X-ray Studies.* The earliest study is dated February 27, 1944, and showed normal lung with a small oval calcified deposit at right base. On March 13, 1944, evidence of a pneumonic process in the left lower lobe with pleurisy and effusion is recorded. A definite change is noted in the appearance of the heart in the upright and prone positions, apparently due to a small amount of pericardial fluid causing a widening about the base of the heart. Film of the chest on May 20, 1944, shows small calcified parenchymal scar in lower right lung with small calcified nodes at the right hilum. Impression of film taken June 16, 1944, was normal chest. On August 11, 1944, *x*-ray showed massive left pleural effusion with mediastinal displacement to right. *X*-ray report of October 23, 1944, revealed fluid extended from apex to base without mediastinal displacement; the December 4, 1944, report stated multiple fluid levels are identified; the February 26, 1945, report revealed pleural thickening in the left hemithorax. There was very slight increase in the transverse diameter of the cardiac shadow.

*Serial Electrocardiographic Changes.* First electrocardiogram taken February 29, 1944, approximately three weeks after admission overseas, revealed slightly low and rounded T-waves. Another electrocardiogram four days later revealed further slight decrease in the voltage of the T-waves. It was during this time that a pericardial friction rub and a soft blowing systolic murmur were noted. An electrocardiogram taken May 19, 1944, shortly after admission to Billings General Hospital, showed a return of T-waves to normal amplitude. At this time, examina-

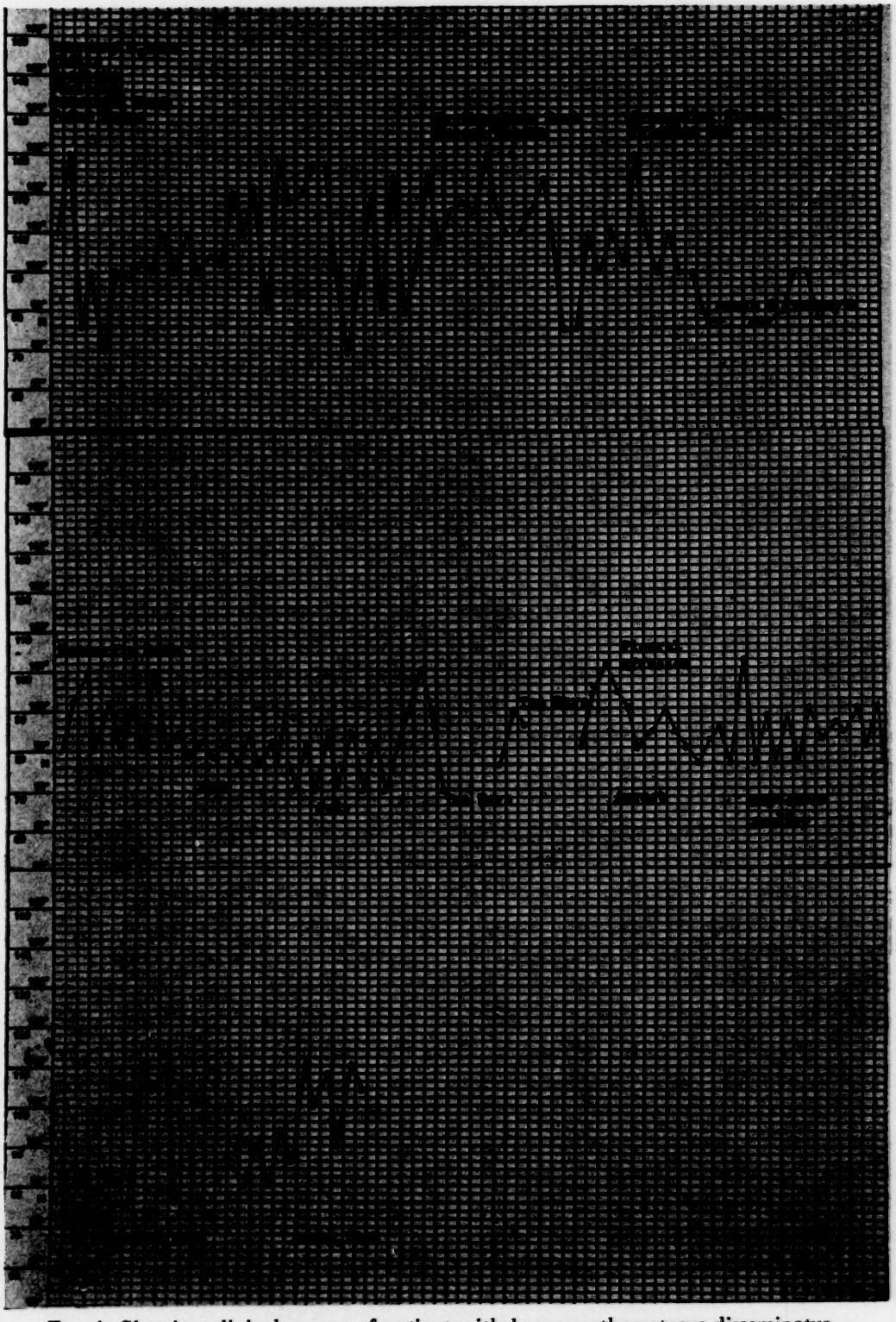


FIG. 1. Showing clinical course of patient with lupus erythematosus disseminatus.

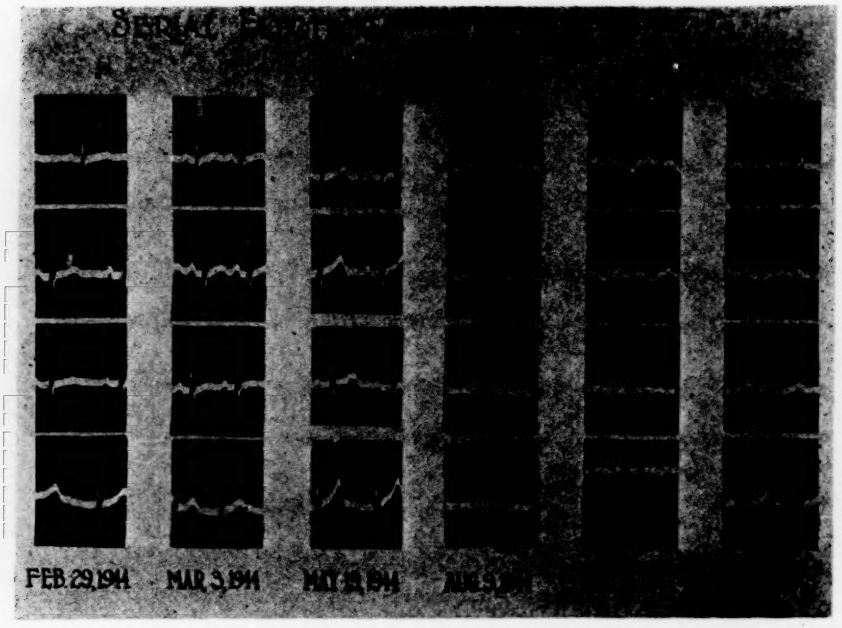



FIG. 2

tion of the heart and lungs was negative. During August, 1944, the patient developed a massive left pleural effusion with a shift of the mediastinum to the right. All the QRS complexes and the T-waves in leads I and II were diminished in amplitude and in leads III and CF-IV were almost isoelectric. The heart sounds were very distant due to the massive left pleural effusion and the right border of the heart showed pulsations of good amplitude on fluoroscopic examination. At this time it was believed that the diminished QRS complexes and low T-waves were at least partly due to the massive pleural effusion. On December 4, 1944, further changes were noted and T-I and T-II had become deeply inverted, T-III was diphasic and T in CF-IV was deeply inverted. An electrocardiogram on February 14, 1945, revealed T-I still inverted with T in leads II, III and CF-IV upright. The last three serial tracings are compatible with a pericardial effusion and the subsequent development of a thickened pericardium. (Fig. 2.)

*Treatment.* During the first three weeks of his illness the patient received sulfadiazine in standard doses. Sodium salicylate was substituted for the sulfa and continued until his arrival to the United States. Here his orders read, "Complete bed management; high caloric, high protein diet; sodium salicylate Gm. IV in divided doses; multi-vitamin capsule t.i.d.; and 3 cc. liver extract tri-weekly." In August, it was decided to give him a course of penicillin consisting of 1,500,000 units, which had no effect on the course of his disease. He felt more comfortable when on salicylates. The mouth lesions were very resistant to treatment and ran their course uneffected by any therapy tried, such as topical sulfa, penicillin, and all the usual mouth washes. Plasma and washed cells were given in the latter part of the course.

## AUTOPSY REPORT

*General.* The skin over the face was roughened and there was a muddy appearance starting from the area of the nose and extending over almost the entire sides of the face. There was a similar appearance over the sternum but here there were dis-

persed whitish areas. Upon incision the subcutaneous fat was yellow and scant. The muscles were red and well developed. There was a considerable accumulation of yellowish viscid fluid in the abdominal cavity. All organs were in their normal relationship. There were adhesions between the anterior surface of both lobes of the liver and the diaphragm and anterior abdominal wall. The spleen was also adherent to the diaphragm and could be separated with moderate ease. The diaphragm was at the level of the sixth rib on the left and at the fifth on the right. The mesenteric lymph nodes were prominent. The intestines and intra-abdominal fat were edematous; this was more marked in the colon. The diaphragm was also thick and edematous. There were universal adhesions between the visceral and parietal pleura on the left side which completely obliterated the pleural cavity except on the posterior portion where there was considerable fluid. There was a moderate amount of fluid in the right pleural cavity. The mediastinum was in the midline. The pericardium was thick and edematous. There were universal adhesions between the pericardium and the epicardium with a few pockets of inspissated fluid in the cavity. A culture was taken from one of these pockets. The parietal pericardium on the right reached 1 cm. in thickness and could be taken off in the form of a white opaque plaque.

*Lungs.* In the upper portion of the right middle lobe was a small pleural calcific nodule. In the interlobar fissure there was an accumulation of greenish-brown inspissated material. This communicated with a cavity, 15 mm. in diameter, which was filled with similar material and was delimited from the adjacent tissue by a membrane 1 mm. in thickness. The cavity appeared to be in the substance of the upper lobe. The trachea and bronchi were congested. The tracheal-bronchial nodes were enlarged and the one on the left was calcified.

*Heart.* As mentioned previously, the pericardium was markedly thickened and edematous. The heart, with the pericardium and ascending aorta, weighed 780 Gm. The epicardium was also edematous. On the posterior wall of the right ventricle was an irregular area of thickened gray endocardium. In the angle made by the origin of the chorda tendineae of the posterior leaflet of the valve and the ventricle wall, there was a flattened rough granular vegetation, some of which extended on to the chord. There was slight fusion between the anterior and left cusps of the pulmonary valve. There was considerable hypertrophy of the left ventricular wall. There were large scattered areas of thickened and gray endocardium throughout the ventricle but more marked about the base of the papillary muscles and behind the leaflets of the mitral valve. At the base of the papillary muscle of the anterior leaflet of the mitral valve was a flat vegetation 1 cm. in diameter. Scattered over the endocardium at the apex were numerous small areas of roughening with some small vegetations. Some of the chordae tendinae of the mitral valve were short and thick and an occasional one had a fusiform thickening. On the anterior surface of the anterior leaflet of the mitral valve was another flat vegetation. In the commissure between the left and right cusps of the aortic valve there was a small vegetation and another was present between the right and left posterior cusps. The left auricular appendage was not enlarged but the communication with the left auricle was difficult to trace because of edema about the ostium. The ostium permitted a probe to enter.

*Spleen.* The spleen weighed 480 Gm. The capsule was roughened by the adhesions mentioned above and in the capsule there were diffuse areas of thickening which appeared white and opaque. On the cut

surface the follicles were prominent and the pulp did not scrape.

*Liver.* The liver weighed 2,350 gm. The capsule had areas of roughening corresponding to the adhesions mentioned above. On cut surface the lobular markings were indistinct but in places were discernible. The *gallbladder* and pancreas were normal.

*Adrenals.* The periadrenal tissue was markedly edematous. The adrenals together weighed 25 Gm. On cut surface there was a normal proportion of cortex and medulla.

*Gastro-intestinal Tract.* The gastrointestinal tract and the mesentery were edematous. There were a few small hemorrhages in the middle third of the jejunum. The mesenteric lymph nodes were prominent but not much enlarged.

*Genito-urinary Tract.* Both kidneys were of equal size and together weighed 400 Gm. There was marked edema of the perirenal tissue. The capsule stripped with moderate ease revealing a surface which was mottled with deep brown and yellow areas. The brownish area appeared to be slightly depressed. A few hemorrhages, slightly larger than a pinpoint, were present and numerous small hemorrhages were seen in the capsule. On cut section the cortical markings were discernible, but with difficulty. The periureteral tissue was markedly edematous. The ureters were patent throughout and not dilated.

The *bladder*, *seminal vesicles*, *prostate* and *testicles* were normal.

MICROSCOPIC

*Heart (Posterior Mitral Valve); Pericardium.* Pericardium was thickened and edematous. There was an increase in supporting connective tissue and a considerable portion of the collagen was intensely eosinophilic. There were numerous monocytic cells with basophilic cytoplasm; some had a nucleus resembling that of a myocyte.

*Myocardium.* There was separation of muscle fibers with a fine fibrillar connective tissue between them. Muscle bundles often were separated by a dense thick straight fibrous tissue, which was densely eosinophilic. This was also present, though more irregular, in perivascular zones. Occasional areas showed loss of muscle fibers and here and there were collections of polys, monocytic and fibroblastic cells. A considerable quantity of eosinophilic collagen was present in the region of the mitral ring.

*Endocardium.* The endocardium was thickened and vascularized and contained numerous macrophages with iron pigment as well as monocytic cells with eosinophilic cytoplasm, fibroblasts and an occasional multinucleated cell. The chordae tendinae were fused in the endocardial reaction.

*Mitral Valve.* The mitral valve was vascularized throughout the length of the auricular portion and much of the collagen was intensely eosinophilic.

*Right Ventricle.* The myocardium showed more pronounced intermuscular changes than in the MVP section. The endocardium showed more fibrosis and thickening, but in addition there was an acute mural vegetation composed of slightly basophilic irregular homogeneous material which resembled somewhat the collagen changes in the myocardium. In the meshes were red cells, delicate fibrillar reticulin, and occasional vacuolated cells. A chorda tendinae here also was fused in the endocardial change. The older endocardial changes extended into the septa between the myocardial fibres. There were blood vessels with the muscle fibres swollen and vacuolated with marked narrowing to almost complete occlusion of the lumen. There were bluish bodies in some of the capillary lumina which appeared like basophilic bodies described in the mural lesions of Lupus Erythematosus. In some sections, focal collections of polys and edematous blood vessel walls were found.

*Lung.* There was considerable congestion and scattered collections of mononuclear and septal cells containing pigment in the alveoli. In some areas the alveoli were filled with red blood cells and edema fluid as well as a few mononuclear cells and polys. In places the blood was hemolyzed. There were a few groups of alveoli and an occasional bronchiole filled with polys and mononuclear cells. A few small areas of atelectasis were also seen. In some places the alveolar septa were thickened. Occasionally, a larger vessel showed an eosinophilic wall. One large vein contained nuclear débris in the wall and thrombus. Other veins showed a similar change without thrombus. Sections of the subpleural abscess showed little inflammatory reaction around it. At its periphery was a moderate sized vein with a recannalized lumen. The visceral pleura was thick and edematous containing a few round and plasma cells. One localized collection of polys and mononuclear cells was seen in it. The parietal pleura was hypervascular and edematous. The collagen was swollen. There were scattered mononuclear cells with basophilic cytoplasm, and focal collections of round cells. The collagen of some of the vessels and perivascular areas appeared swollen. In these regions monocytic cells were present.

*Diaphragm.* There was marked edema and a few round and plasma cells were present. In addition, there were a number of mononuclear cells with basophilic cytoplasm. These were scattered through the tissue but were concentrated near the pleural surfaces. The collagen in the subserosal and perivascular areas was swollen.

*Liver.* The architecture was not disturbed. In places the capsule was thick and edematous and contained a few round and plasma cells. The portal veins were dilated. In the portal areas there were vacuoles in the liver cells.

*Gallbladder.* There were thickened arteries and autolysis.

*Spleen.* The capsule was thickened. The sinusoids were distended with blood and in places the pulp was hemorrhagic. There was periarteriolar fibrosis in the follicles. The septa were prominent. There was a calcific fibrotic nodule close to the capsule. A few collections of lipoid laden cells were seen in the pulp, with considerable numbers subcapsular in location.

*Pancreas.* There was a rare focus of atrophy with collections of mononuclear cells and histiocytes. In places the capsular and septal collagen appeared swollen.

*Small Intestine.* The serosa was edematous and contained mononuclear cells. The arterioles were thickened, particularly in the submucosa. Some of these were hyalinized.

*Adrenal.* The periadrenal tissues were edematous. The capsule was thickened. The collagen was swollen. Focal cortical areas contained considerable lipoid.

*Kidney.* Numerous glomeruli showed "hyaline thrombi" in the tuft. "Wire loop" lesions were not numerous. The cells of some of the tufts had considerable cytoplasm which seemed to occlude the lumen, rendering the glomerulus anemic. Some of the cortical arterioles contained thrombi. One medium sized vein contained a thrombus. The tubules contained granular material and a few contained hyalin casts. Here and there was a focal collection of mononuclear cells.

*Prostate.* An occasional artery was edematous.

*Testicle.* Spermatogenesis was active but few mature spermatozoa were seen. There was an increase in the interstitial cells.

*Muscle.* Sections of voluntary muscle revealed pronounced atrophy, degenerative changes and necrosis of the muscle fibers. Some of the fibers were multinucleated. There were focal areas containing mono-

nuclear cells and cells resembling endomysial cells. There was considerable amounts of fine fibrillar reticulin between the muscle fibers. Areas of fibrosis were present.

*Lymph Nodes.* The general architecture was not disturbed. Here and there the sinusoidal walls were thick and hyalin and occasionally a small artery contained a "hyalin thrombus." There were several areas in which there were groups of slightly basophilic large "hyalin" material, apparently in dilated sinusoids and surrounded by areas of necrosis. There were other areas of necrosis and a few areas containing polys. Macrophages with nuclear debris and red cells were present, usually about the necrotic lesions. About some nodes the tissue showed changes similar to those in the periadrenal tissue.

SUMMARY

A case of lupus erythematosus disseminatus in a male with a clinical course of approximately seventeen months was reported.

The onset was with polyarthralgia, "Erythema Multiforme," pleural and pericardial involvement. Later a butterfly rash developed. The patient was intermittently febrile. Late in the course he developed a systolic murmur and gallop rhythm. Renal involvement appeared clinically in the thirteenth month of the disease.

Autopsy revealed thickened serous surfaces, small endocardial vegetations of the Libman-Sacks type, collagen changes throughout the body involving blood vessels, muscles, serous membranes and endocardium. Kidney sections revealed "hyalin thrombi" with a few "wire loop" lesions of the glomeruli.

# Purulent Pericardial Effusion

MEYER TEXON, M.D.
NEW YORK, NEW YORK

MASSIVE purulent pericardial effusion is of sufficient clinical and academic interest to warrant the following case report:

A forty-six-year old white male was admitted to the Knickerbocker Hospital Medical Ward on October 9, 1944, complaining of fever, diffuse aches, non-productive cough and chills of five days' duration. The history revealed excessive alcoholism for about fifteen years, together with a diet lacking sufficient meats and greens. The physical examination upon admission disclosed herpes of the lips and a furry tongue having red, atrophic margins. A few crepitant râles were heard over the right lower lobe in the paravertebral area. The heart sounds, size and rhythm were normal. Blood pressure was 122/80, pulse 100 per minute. The liver was enlarged to two fingerbreadths below the costal margin. No spleen was palpable. The skin was hot and dry. The body hair was sparse. A few facial telangectases were noted. The nail beds were cyanosed. There was no jaundice. The laboratory data upon admission included: temperature 103°F., red blood count 4.7 million, hemoglobin 14.5 Gm., 100 per cent, white blood count 21,000 with 96 per cent polymorphonuclears, and 4 per cent lymphocytes. Urinalysis revealed specific gravity 1.030, acid, albumin 2 plus, sugar negative, with occasional fine granular casts. An *x*-ray of the chest on the day of admission revealed "no evidence of any pulmonary infiltration or consolidation. The heart is within normal limits of size and configuration." The admitting diagnosis was right lower lobe pneumonia, and chronic alcoholism with liver cirrhosis and avitaminosis.

From Figure 1 depicting the course, it may be noted that 22 Gm. of sulfadiazine administered during the first four days had no appreciable effect on the sustained fever. Penicillin, 20,000 units every three hours, was then given for the next nine days, the total dose amounting to 900,000 Oxford units. Sulfadiazine to a total of 76 Gm. was continued at the same time until the fourteenth day; 3,000 cc. of 5 per cent glucose in normal saline was administered intravenously on the fourth day. Thiamine chloride in doses of 100 mg. was given by vein on the third and fourth day, then resumed on the fourteenth day and repeated daily thereafter. On the fifth day the second chest *x*-ray showed "no pulmonary change" but the heart shadow appeared slightly enlarged. Clinically, the patient claimed to be feeling better but objectively he appeared acutely ill and drowsy. Repeated chest films (Fig. 2) on the eleventh, fifteenth, eighteenth, and twenty-fourth days showed progressive increase in the size of the heart shadow. Electrocardiograms (Fig. 3) on the sixteenth and twenty-second days showed changes consistent with pericardial effusion. On the thirteenth day pericardial paracentesis yielded about 15 cc. of a serosanguineous fluid. On the fourteenth day large doses of aspirin were given in an effort to lower the temperature. The signs in the lungs seemed to clear entirely. The heart sounds continued to be good with no pericardial rub, gallop or murmurs audible. The blood pressure remained about 140/80 on the day of the pericardial tapping. On the twentieth day there appeared a persistent systolic blowing murmur at the apex. On the thirteenth day the patient continued to claim "improvement" although he appeared weaker and the skin showed increasing pallor. The apical murmur persisted but no pericardial rub or petechiae were noted. The circulation time was normal (18 seconds) on the seventeenth day. A transfusion, 500 cc. of whole blood, was given on the thirty-first day, the red blood count having dropped to 3.65 million and the hemoglobin to 71 per cent, 10.2 Gm. On the thirty-third day

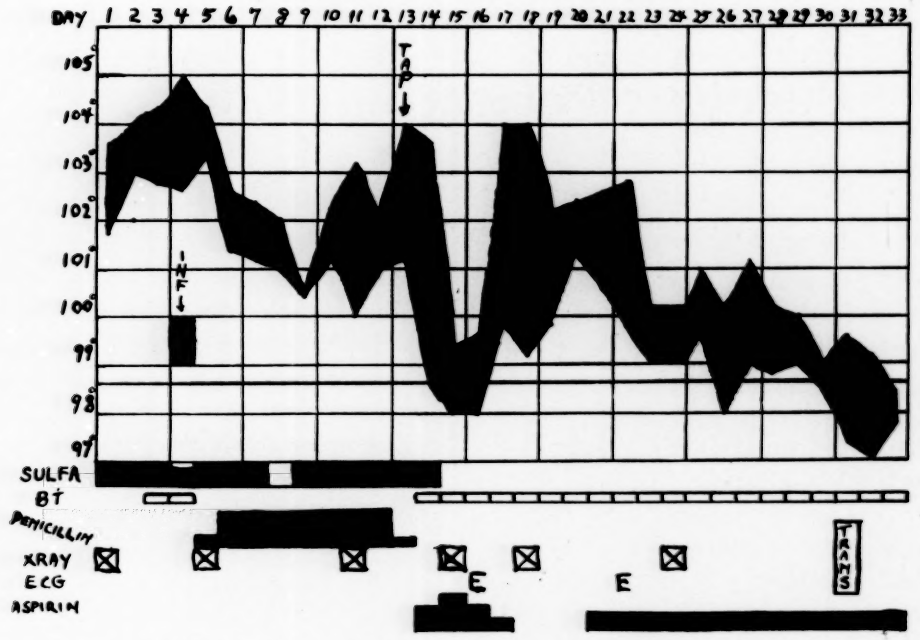



FIG. 1. Chart depicting the course of the disease.

the patient expired having become progressively more cyanotic with a rapid, thready pulse and muffled, indistinct heart sounds.

Additional data included negative Kahn and Kline tests. The pericardial fluid revealed 300,000 red blood cells per c. mm., 3,400 white blood cells per c. mm., (all lymphocytes). The smear revealed no organisms. Culture produced hemolytic staphylococcus aureus. Postmortem cultures from the pericardial effusion produced hemolytic streptococci, hemolytic bacillus coli and pneumococci type VII.

The necropsy performed by Dr. Joseph Ballinger revealed the following: The heart is approached through an abdominal incision so that the shape and size are not discernible. The pericardial sac is markedly distended with turbid seropurulent fluid of moderate viscosity, measuring 1,500 cc. in volume. In two places the two layers of the pericardium are firmly and densely adherent. One of these is at the apex and adjacent left lateral border over an area 5 by 6 cm., the other layer over the anterior septum occupied an area 3 by 1.5 cm. These adhesions are inseparably attached and represent an old process. Elsewhere the pericardial sac is filled with the above described fluid. The two internal surfaces of the pericardium are covered with a mass of shaggy, fibrinous, tannish-brown, friable adhesions measuring up to 1 cm. in thickness. In one focus along the posterior wall of the left ventricle, directly above the apex, there is a 1 by 1 cm. cheesy abscess directly above the myocardium and beneath the epicardium. The myocardium is flabby, pale, tannish-grey in color, parboiled in appearance, and measures 9 mm. at its thickest portion of the left ventricle and 2 to 3 mm. in the right ventricle. The endocardial surface of the chambers of the heart are pale, smooth, glistening and free from change. All orifices are normally patent, and all valves, save for the aortic, are free from gross change. The aortic valve presents a marked fusion of all its commissures in places measuring up to 1 cm. at the point of fusion. The cusps are slightly thickened and their free edges slightly rolled. There are no verrucae on any of the cusps. Instead there is a single, soft, pink, smooth, fleshy vegetation 7 by 5 by 5 mm. on the ventricular surface of the commissural junction between the right and left cusps. There is no surrounding or underlying ulceration of the cusps. The foramen ovale and ductus arteriosus are obliterated. The coronary ostia and their arteries are everywhere smooth, glistening and widely patent. The vena cavae are grossly normal.

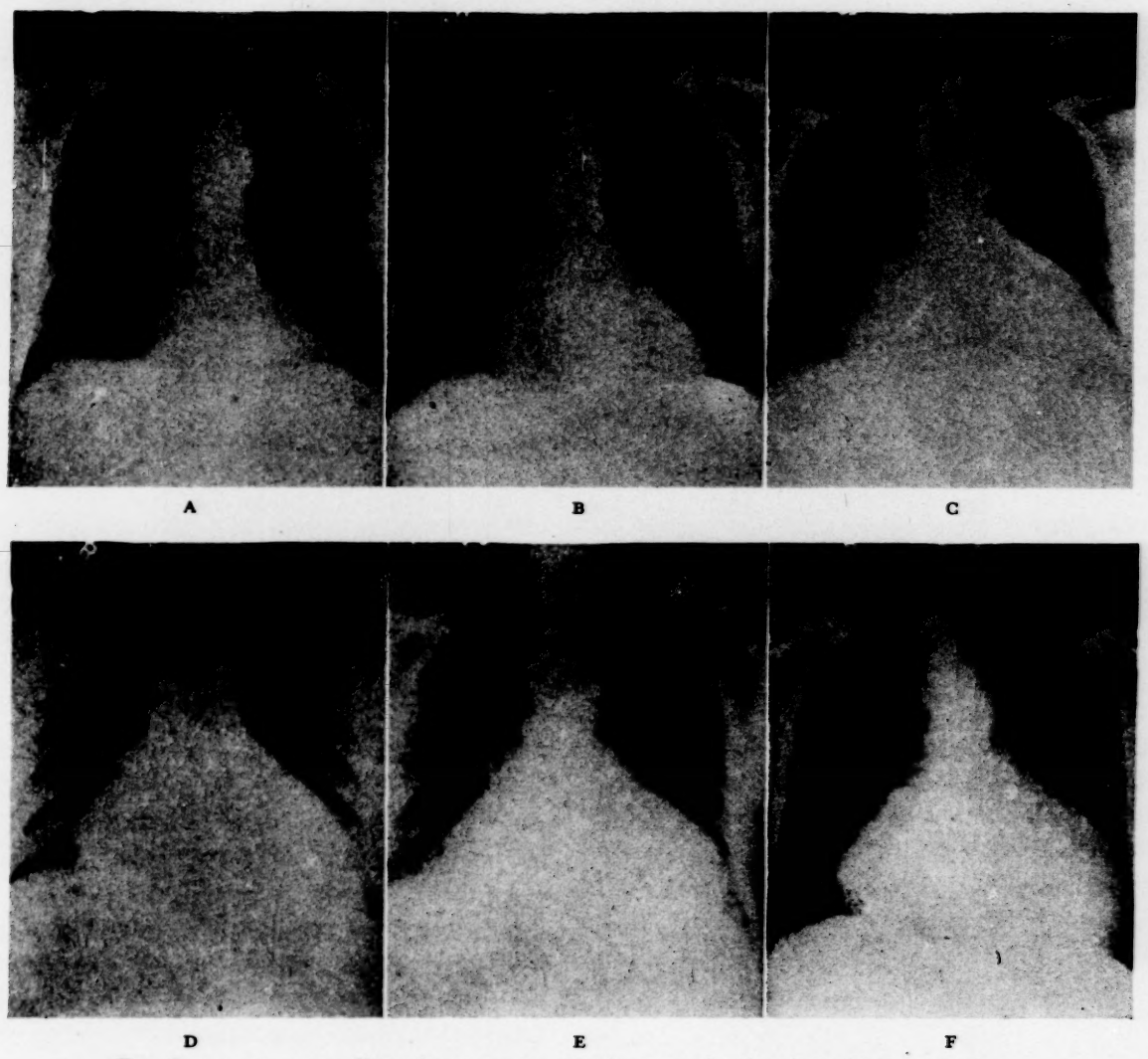



FIG. 2. A to F, *x*-ray films show progressive increase in the size of heart shadow.

Microscopically, the fibers are somewhat swollen by the moderately severe parenchymatous degenerative changes. The epicardial surface is fibrously thickened and covered with a thick coat of inflammatory reaction, the base of which is already densely fibrous and vascularized (non-specific chronic granulation tissue). The uppermost layers of the coat are composed of an acute fibrinopurulent exudate. Plasma cells and phagocytosed blood pigment are noted in the deeper fibrosed portion of the epicardial coat. No evidence of tuberculosis is seen. The grossly described cheesy abscess in the subpericardial zone represents a purulent non-specific abscess showing early walling off by granulation tissue in which there are a few non-specific multinucleated giant cells.

There is no evidence of consolidation, infarction or hemorrhage in any portion of the lung.

There is marked distention and engorgement of the central veins and sinusoids of the liver with early fatty metamorphosis of the peripheral zone of hepatic cells. Grossly the liver weighed 2,260 Gm. The external surface is smooth, glistening and brownish tan. The organ cuts with normal resistance to present a nutmeg appearance of reddish-brown areas surrounded by paler tan areas representing passive congestion. The remainder of the organs revealed no unusual changes.

The final diagnosis was massive serofibrinopurulent pericardial effusion; congenital or rheumatic commissural fusion of the aortic

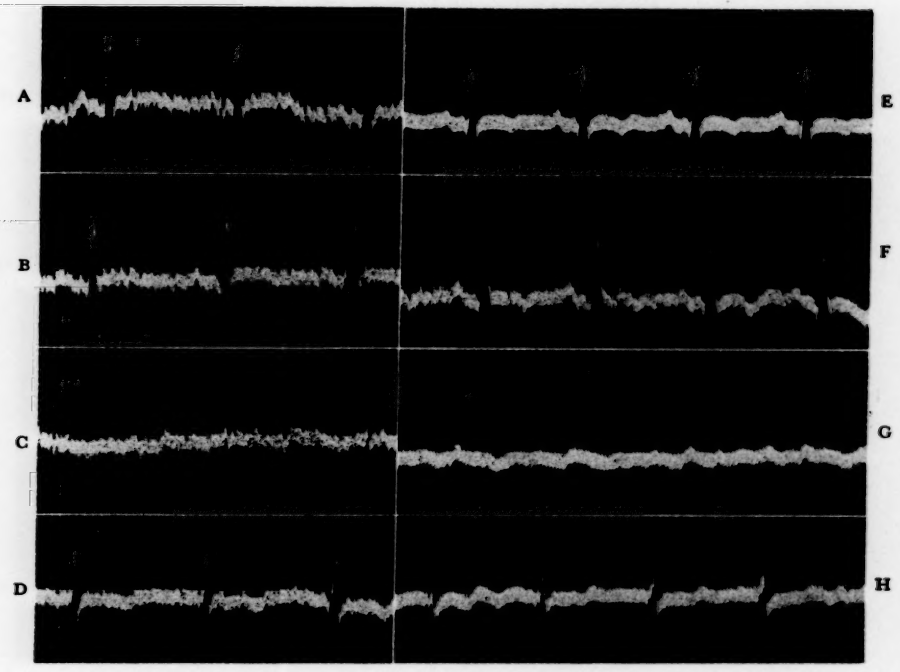



FIG. 3. A to H, electrocardiograms show changes consistent with pericardial effusion.

cusps, with superimposed recent vegetation (thrombotic, non-bacterial, vegetative endocarditis); and chronic passive congestion of the liver.

## COMMENTS

The diagnosis of pneumonia upon admission was justified clinically although not visualized by *x*-ray. This may have been due to a retrocardiac position of the process. The involvement of the pericardium must be presumed to have occurred by contiguity. The therapy might have included penicillin instilled directly into the pericardial sac. The incidental finding at necropsy of a rheumatic heart with aortic valvular involvement and vegetation again points out the frequency with which this occurs without obvious clinical signs or symptoms. It is believed that the cause of death was toxemia from the massive purulent pericardial effusion. Also, the patient, an alcoholic, did not resist the infection with normal constitutional powers.

## SUMMARY

A fatal case of purulent pericardial effusion in which the patient was treated with sulfadiazine and penicillin is presented.

# Editorial

## Vivax Malaria and the 8-Aminoquinolines

Should it happen, as now seems likely, that generally useful curative agents for vivax malaria are contained in the series of 8-aminoquinolines, this will make an interesting chapter in the development of chemotherapeutic agents. Pamaquine was first used in the late 1920's and early 1930's on a very extensive scale. It was said, on the basis of these early studies, to possess some *suppressive* activity, as evidenced by its effect upon the erythrocytic phase of vivax malaria, as well as *curative* activity in this disease. It was also said to have little or no *suppressive* activity in falciparum malaria but a dramatic effect upon the gametocytes of the plasmodium responsible for this infection. In addition, it was said to have a true *prophylactic* action in each infection.

Shortly after the drug was available for large scale experimental use, it became apparent that the dosage recommended in the earlier studies could be expected to produce widespread and seriously toxic effects. However, the extent of the toxicity was not appreciated at a sufficiently early date to prevent the organization of reasonably well controlled trials to assay the *curative* action of pamaquine in vivax malaria.

It was common practice at that time, i.e., around 1930, to treat both vivax and falciparum malaria with full therapeutic doses of quinine, about 2.0 Gm. daily, for some fourteen to twenty-eight days. Consequently, when pamaquine was tested it was also administered for this period of time. It was demonstrated quite early that a combination of concurrently administered pamaquine and quinine is superior to the administration of either drug alone. For example, in one series there was observed 75 per cent relapses in an eight-week period with quinine alone, 25 per cent with pamaquine alone and essentially none with a combination of the two antimalarials. The dosage of pamaquine in these studies, calculated as the hydrochloride, was as low as 40 mg. daily in some patients. It is possible that such a dosage regimen would have come into general use despite the toxic effects of the pamaquine except for the discovery and limited exploration of quinacrine which occurred about this time.

It was found that little advantage is derived from the administration of quinacrine beyond a seven-day period of treatment at 0.1 Gm. three times a day in population groups having a fair degree of immunity. As a reaction to this finding, it was thought that the course of quinine therapy might also be shortened with advantage. This belief, together with a growing appreciation of the toxic hazard of pamaquine, led to a curtailment in the duration of the administration of quinine and a lowering of the pamaquine dosage commonly used. It is not surprising, then, that the publications of the League of Nations recommended that combination pamaquine and quinine therapy be limited to seven days with the daily dose of pamaquine no higher than 30 mg. of the hydrochloride daily. The increase in the toxicity of pamaquine when administered concurrently with quinacrine led to the adoption of a convention whereby pamaquine was administered in similar dosage but for only five days and separated from quinacrine administration by a three-day drug-free interval.

It is now known that pamaquine admin-

istered at such a dosage and in such a manner has little to offer as a curative agent in many vivax malarias although it is a highly effective gametocidal agent. It seems likely that the early studies with pamaquine produced a different therapeutic result because the dosage was usually higher, administration was for a longer period of time, and the drug was administered concurrently with quinine. However, all three features were lost sight of in the years between 1931 and 1941 so that the early recommendations for the use of pamaquine by the services were not of the type that would be expected to yield a significant proportion of cures.

The study of pamaquine in the O.S.R.D. program involved, first, the demonstration that it does possess a truly prophylactic action, as previously defined, in both vivax and falciparum malaria. It was then shown that of the manifestations of pamaquine intoxication, which had been described, only the acute hemolytic anemias were of serious consequence and these do not occur or are rare in the white individual. This having been established, the further study of pamaquine and related substances was limited to this type of patient. It was then demonstrated beyond doubt that pamaquine does have a *curative* action when administered concurrently with quinine for fourteen days in vivax malaria due to either domestic or southwest Pacific strains. Having confirmed these essential facts relating to the antimalarial activity of pamaquine, it was further demonstrated that *prophylactic* and *curative* activity are characteristics of a class of compounds, i.e., derivatives of 6-methoxy-8-aminoquinoline, and not of only one member of the class.

A systematic survey of 8-aminoquinolines for curative action in vivax malaria was then organized in a fashion which permitted the screening of a relatively large number of compounds with safety and with a fair chance of selecting any very promising compound. It was assumed on the basis of the evidence then available that: (1) the maximal tolerated daily dose of pamaquine, when given in conjunction with quinine, is in the order of 90 mg. of pamaquine base; (2) since pamaquine produces symptoms of intoxication with daily doses of 30 mg. of base, or one-third the maximal tolerated dose, a generally useful 8-aminoquinoline would have to be effective at one-sixth the maximally tolerated dose; (3) one could predict the maximal tolerated dose of an 8-aminoquinoline in the human within a factor of two on a limited series of toxicity studies in the monkey; (4) it was possible to screen out, in toxicity studies in the monkey, compounds producing the irreversible type of central nervous system damage which characterizes plasmocide toxicity.

On the basis of these assumptions, 8-aminoquinolines were selected for clinical trial if they did not possess the plasmocide type of toxicity and if they were no more toxic than pamaquine. They were tested in combination with quinine in mosquito-induced Chesson vivax malaria at a daily dosage of one-sixth their calculated maximal tolerated dose. Combined drug administration was for fourteen days in all cases.

Studies of this general type were conducted during the last year of the O.S.R.D. program and are continuing in the present U.S.P.H.S. program. This much can be said with certainty. Pamaquine is not the best 8-aminoquinoline for use in the cure of vivax malaria. Pentaquine, 8-(5-isopropyl-aminoamyl-amino)-6-methoxyquinoline, is a superior drug for this purpose and probably generally usable if moderate precautions are taken.[1] However, whether it is the best which will be developed in the series is less certain.—JAMES A. SHANNON, M.D.

[1] LOEB, R. F., Chairman of Board for Coordination of Malarial Studies. Activity of a new antimalarial agent, Pentaquine (SN 13,276). *J. A. M. A.*, 132: 6, 1946.

# handle it delicately . . .

**In abdominal surgery the bowel is handled as gently as possible to avoid even the slightest traumatism.**

**In constipation management the same delicacy is desirable—harsh, irritant cathartics and purgatives are replaced by the more physiologic method of "Smoothage."**

**Metamucil provides "Smoothage" —soft, bland, mucilloid bulk devoid of chemical and physical irritants.**

**Metamucil is the highly refined mucilloid of a seed of the psyllium group, Plantago ovata (50%), combined with dextrose (50%).**

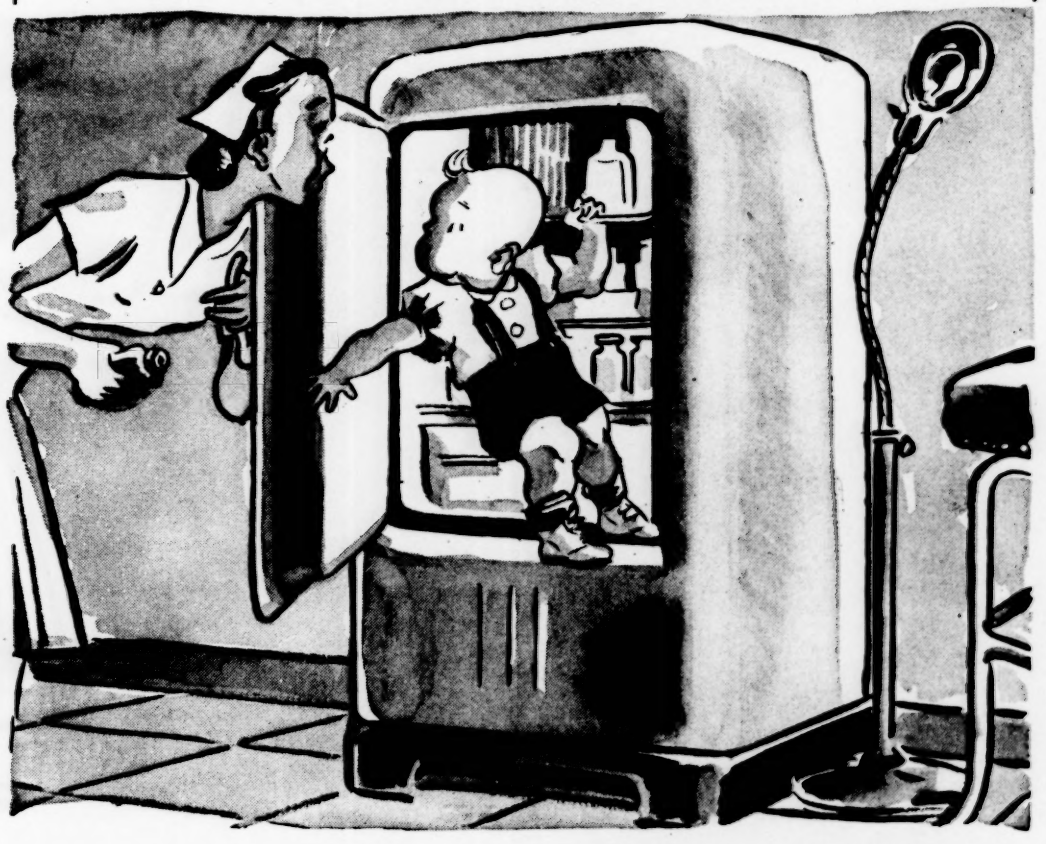
Metamucil is the registered trademark of G. D. Searle & Co., Chicago 80, Illinois

**SEARLE**

ACCEPTED AMERICAN MEDICAL ASSN.

RESEARCH IN THE SERVICE OF MEDICINE

## "I'm just makin' sure the doctor uses D-P-T!"



### He's pretty smart—to look for better protection and less chance of reaction with Cutter D-P-T

With Phase I pertussis organisms *grown on human blood*, with toxoids *so purified* that each cc. contains far more than a single human dose . . . you avoid heterologous animal protein. Hence, with D-P-T, there is *less* chance for reaction or anaphylactic shock, *more* chance of establishing a high immunity level.

Too, with Cutter D-P-T, the concentration of both pertussis organisms and toxoids allows a more potent dosage in smaller volume. No king-size syringe to outrage mother or little darling. Your dosage schedule with Cutter D-P-T is only 0.5 cc., 1 cc., 1 cc.

Cutter also makes D-P-T (*Alhydrox*), which offers even further advantages. It produces better immunity levels than alum precipitated vaccines. And, because of its more physiologically normal pH, it also presents less pain on injection. Persistent nodules and sterile abscesses are rare, rather than an expected contingency.

D-P-T works to your advantage, as well as your patients'. Try it in your practice, won't you?

Cutter Laboratories, Berkeley, California
Chicago · New York

CUTTER

Fine Biologicals and
Pharmaceutical Specialties

# efficient, low-dosage treatment of ulcerative colitis with 'Sulfathalidine'

***Phthalylsulfathiazole***

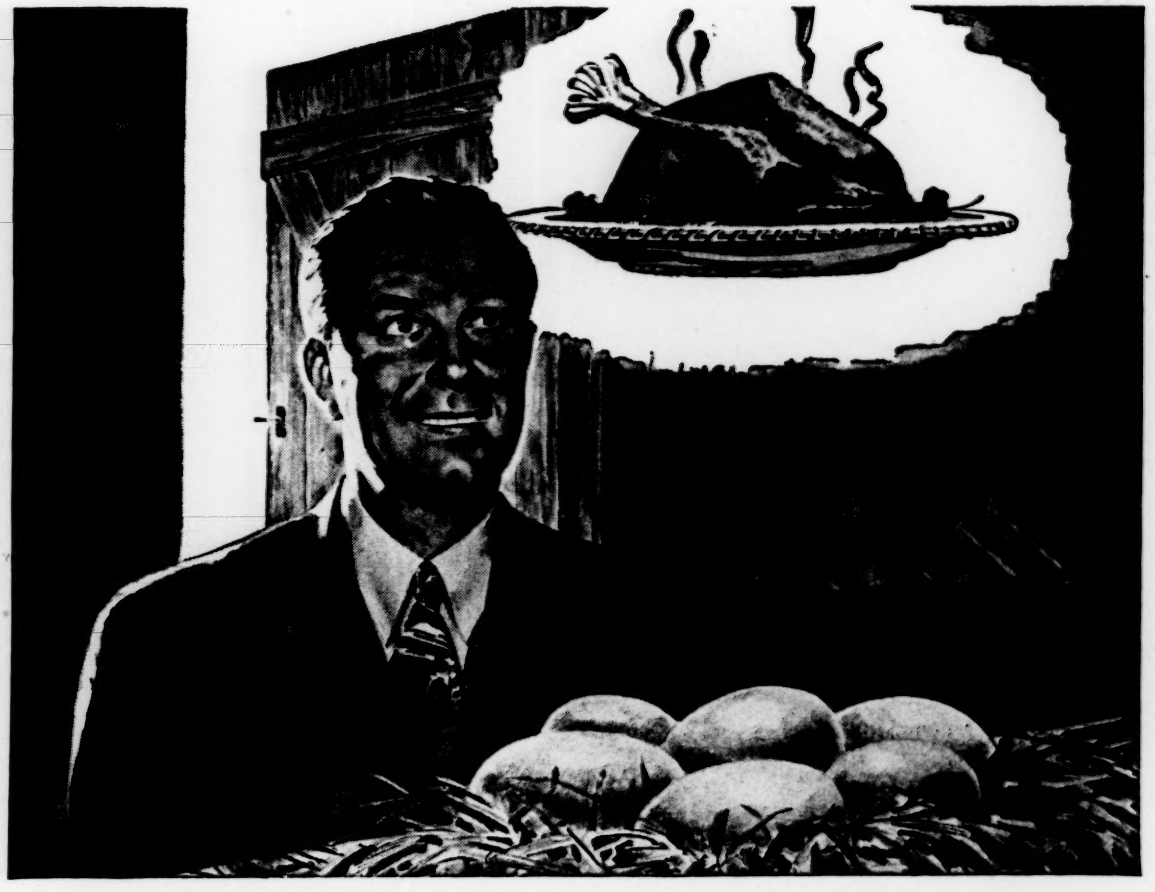
This *nontoxic, low-dosage*, enteric sulfonamide is exceptionally effective against acute and chronic ulcerative colitis, and recently proved successful in the treatment of 76 out of 80 patients[1] with this disease. After therapy with the drug, stools become formed and odorless, blood in stools disappears, cramping in abdomen subsides within 48 hours, and evacuations are reduced substantially.[2]

'SULFATHALIDINE' *phthalylsulfathiazole* is indicated also in the treatment of regional ileitis, as a supplement to the therapy of amebiasis, giardiasis and paratyphoid infections, and as an adjunct to intestinal surgery.

'SULFATHALIDINE' *phthalylsulfathiazole* maintains a *high bacteriostatic concentration* in the gastrointestinal tract (1250 mg. per cent). An average of only 5% of the drug is absorbed from the bowel and this is rapidly excreted by the kidneys. Administered in daily doses of only 0.05 Gm. to 0.1 Gm. per kilogram of body weight. Supplied in 0.5-Gm. compressed tablets in bottles of 100, 500 and 1,000. Sharp & Dohme, Philadelphia 1, Pa.

1. J.A.M.A. *129*:1080, Dec. 15, 1945
2. Illinois M. J. *88*:85, August, 1945

SHARP & DOHME



# Sometimes you can break a good rule!

**It's usually a wise** rule not to plan a chicken dinner before the eggs are hatched.

*But not always!*

If the "chicken dinner" represents your future, and the "eggs" are financial nest eggs—go ahead and plan!

**Especially if** your *nest eggs* are the War Bonds you have bought—and the Savings Bonds you *are buying*. For your government *guarantees* that these will hatch out in just 10 years.

Millions of Americans have found them the safest, surest way to save money . . . and they've proved that buying Bonds on the Payroll Savings Plan is the easiest way to pile up dollars that anyone ever thought of.

**So keep on buying** Savings Bonds at banks, post offices, or on the Payroll Plan.

Then you *can* count your chickens before they're hatched . . . plan exactly the kind of future you want, *and get it!*

**SAVE THE EASY WAY... BUY YOUR BONDS THROUGH PAYROLL SAVINGS**

*Contributed by this magazine in co-operation with the Magazine Publishers of America as a public service.*

The Advertising Council

# Heptuna

## SPEEDIER CORRECTION OF THE HYPOCHROMIC ANEMIA SYNDROME

THE frequent co-existence of hypochromic anemia and multiple nutritional deficiencies has greatly changed the therapeutic approach to the anemia syndrome. In many instances, measures directed solely at raising the hemoglobin level prove totally inadequate. For speedy recovery, and eradication of the many derangements usually associated with secondary anemia, more than iron alone is frequently required.

Heptuna combats the entire anemia syndrome. It supplies not only ferrous sulfate, the most readily available form of iron for hemoglobin synthesis, but also seven essential vitamins, and the B-complex factors of liver and yeast.

Heptuna thus enhances absorption and utilization of iron, stimulates hemoglobin regeneration, and effectively combats many of the systemic disturbances encountered in hypochromic anemia.

**EACH CAPSULE CONTAINS:**

| | |
|---|---|
| Ferrous Sulfate U.S.P. | 4½ Grains |
| Vitamin A (Fish-Liver Oil) | 5,000 U.S.P. Units |
| Vitamin D (Tuna-Liver Oil) | 500 U.S.P. Units |
| Vitamin $B_1$ (Thiamine Hydrochloride) | 2 mg. |
| Vitamin $B_2$ (Riboflavin) | 2 mg. |
| Vitamin $B_6$ (Pyridoxine Hydrochloride) | 0.1 mg. |
| Calcium Pantothenate | 0.333 mg. |
| Niacinamide | 10 mg. |

Together with a Liver Concentrate (Vitamin fraction) derived from 6.5 Gm. fresh liver and dried yeast U.S.P. Not intended for use in the treatment of pernicious anemia.

**J. B. ROERIG & COMPANY**

536 Lake Shore Drive • Chicago 11, Illinois

# *As Appetite Declines*

## WITH THE YEARS

The many somatic and emotional changes encountered in senescence are manifested in a variety of ways, especially by a decrease in appetite. Reduced energy expenditure, atrophic gastric changes, exaggerated food dislikes, and food intolerance all contribute, and not infrequently lead to a state of undernutrition. In older patients, this chain of events can easily produce excessive weakness and impaired stamina, adding to the burdens of senility.

Ovaltine proves an excellent means of preventing these complications. Its wealth of essential nutrients, as indicated by the table of composition, aids in preventing malnutrition. Made with milk as directed, Ovaltine is a delicious food drink. Older patients enjoy it as a mealtime and between-meal beverage, and especially as a bedtime drink. Its low curd tension assures easy digestibility and rapid gastric emptying, hence appetite is not impaired.

**THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.**

# *Ovaltine*

**Three servings daily of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk,* provide:**

| | | | |
|---|---|---|---|
| CALORIES | 669 | VITAMIN A | 3000 I.U. |
| PROTEIN | 32.1 Gm. | VITAMIN $B_1$ | 1.16 mg. |
| FAT | 31.5 Gm. | RIBOFLAVIN | 2.00 mg. |
| CARBOHYDRATE | 64.8 Gm. | NIACIN | 6.81 mg. |
| CALCIUM | 1.12 Gm. | VITAMIN C | 39.6 mg. |
| PHOSPHORUS | 0,939 Gm. | VITAMIN D | 417 I.U. |
| IRON | 12.0 mg. | COPPER | 0.50 mg. |

*** Based on average reported values for milk.**

# Breakfast and the Daily Protein Need

The significance of breakfast in the satisfaction of nutritional requirements has been emphasized in many quarters in the recent past. Breakfast serves to replenish many nutrient stores depleted during the long fast from the previous evening meal, and provides the organism with caloric food energy needed for maximum efficiency during the morning hours. Hence nutrition authorities advise that breakfast should supply from one-fourth to one-third of the daily caloric and nutrient needs.

The morning meal should provide, among other things, its share of the daily protein requirement, since the protein needs must be met daily for proper growth of children and for good nutritional health of adults. In a basic breakfast so widely recommended—fruit, cereal, milk, bread and butter—the protein contribution is significantly high—20.7 Gm., or about 29 per cent of the adult requirement. Not a small amount of this protein is provided by the average serving of cereal (ready to eat or to be cooked), milk and sugar—fully 10 per cent of the adult daily protein need. Thus an important protein contribution is made by the basic breakfast, of which cereals are an integral and universally recommended component.

This average cereal serving also provides B complex vitamins, caloric food energy, and important minerals. Its mixture of proteins is of high biologic value, applicable for the satisfaction of growth and maintenance requirements. Note from the table of composite averages the contribution made by the cereal serving—1 ounce of cereal (whole grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), 4 ounces of milk, and 1 teaspoonful of sugar—and by the basic breakfast.

| | Nutrition Composition of The Basic Breakfast* | Average represented by: cereal, 1 oz.; whole milk, 4 oz.; sugar, 1 teaspoonful |
|---|---|---|
| Calories | 611 | 202 |
| Protein | 20.7 Gm. | 7.1 Gm. |
| Fat | 19.0 Gm. | 5.0 Gm. |
| Carbohydrate | 89.4 Gm. | 33.0 Gm. |
| Calcium | 0.465 Gm. | 0.156 Gm. |
| Iron | 3.0 mg. | 1.6 mg. |
| Vitamin A | 1074 I.U. | 193 I.U. |
| Thiamine | 0.52 mg. | 0.17 mg. |
| Riboflavin | 0.87 mg. | 0.24 mg. |
| Niacin | 2.3 mg. | 1.4 mg. |
| Ascorbic Acid | 64.8 mg. | |

*Orange juice, 4 oz.; cereal, 1 oz.; milk, 4 oz.; sugar, 1 tsp.; bread (enriched, white), 2 slices; butter, 1 tsp. (5 Gm.); milk, 8 oz.

*The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.*

CEREAL INSTITUTE, INC.

135 SOUTH LA SALLE STREET • CHICAGO 3

# A Non-Systemic Antacid and Protective

IN peptic ulcer, Kamadrox affords rapid relief of epigastric discomfort and prompt objective improvement. It promotes healing of the ulcer crater because of the specific influence of its three ingredients (*Magnesium Trisilicate,* 50%; *Aluminum Hydroxide,* 25%; *Colloidal Kaolin,* 25%).

Kamadrox exerts prompt, profound, and sustained acid-combining power. Yet it is systemically inert so that it cannot lead to alkalosis or secondary acid-rise. By forming a coating over the ulcer crater, it provides mechanical as well as chemical protection. Kamadrox is astringent, demulcent, and adsorbent. Its ease of administration and pleasant taste are appreciated by the patient and assure his cooperation in carrying out the ulcer regimen.

# KAMADROX

**KAMADROX POWDER** is supplied in 4-oz. and 1-lb. jars.

**KAMADROX TABLETS** are supplied in bottles of 100, 500, 1,000 and 5,000. Each tablet contains: *Magnesium Trisilicate,* 4 gr.; *Aluminum Hydroxide,* 2 gr.; *Colloidal Kaolin,* 2 gr.

**KAMADROX LIQUID.** Each fluidounce represents 64 gr. (4.15 Gm.) magnesium trisilicate and 32 gr. (2.1 Gm.) kaolin colloidal, suspended in 3½% aluminum hydroxide gel, aromatics, q.s.

**THE S. E. MASSENGILL COMPANY**

**Bristol, Tenn.-Va.**

NEW YORK • SAN FRANCISCO • KANSAS CITY

SEMCO

# *A Single Injection...*

## and effective blood levels for

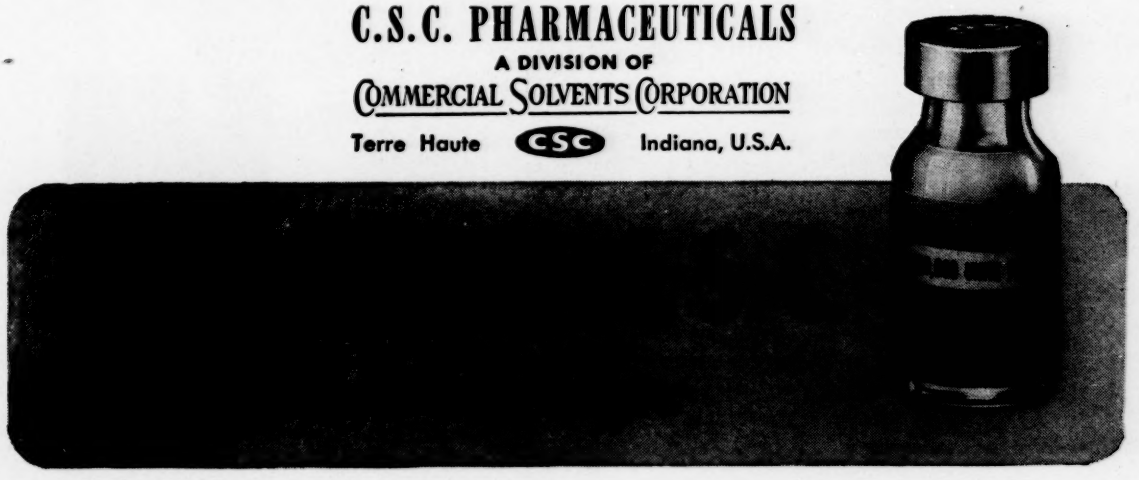
# 24 hours

CLINICALLY effective penicillin blood levels are readily produced and maintained for 24 hours by a single 1 cc. (300,000 units) intramuscular injection of Penicillin-C.S.C. Romansky Type. With the inconvenience of multiple daily injections overcome, the need for hospitalization is frequently obviated, since one visit daily by the physician suffices.

The relatively high penicillin blood levels produced by Penicillin-C.S.C. Romansky Type make this preparation applicable not only in the treatment of gonorrhea, but also in all other infectious diseases due to penicillin-sensitive organisms, except when unusually high doses are required, as in subacute bacterial endocarditis, or when specific administration is indicated, such as intrathecal injection in meningitis.

For rapid liquefaction of contents, vial may be immersed in boiling water without penicillin deterioration. Available in 10 cc.-size serum-type vials, each cc. containing 300,000 units of Penicillin-C.S.C. Crystalline Potassium Salt in a peanut oil-beeswax mixture.

**C.S.C. PHARMACEUTICALS**
A DIVISION OF
COMMERCIAL SOLVENTS CORPORATION
Terre Haute CSC Indiana, U.S.A.



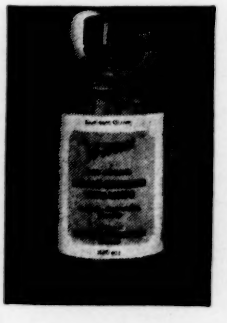
The Margin of Safety
Steel-toed shoes, now available for industrial workers, supplement other safety measures by protecting from falling objects . . . a very effective extra margin of safety.

Similarly, there is a margin of safety, well beyond optimal needs of children, in *Vi-teens Homogenized Vitamins* (especially palatable in milk, water, juice or formula). Full size sample package for physicians upon request.

**One teaspoonful (5 cc) of Vi-teens Homogenized Vitamins contains the following:**

| | |
|---|---|
| Vitamin A (from fish liver oils) | 3000 U.S.P. Units |
| Vitamin $B_1$ | 1 Milligram |
| Vitamin $B_2$ | 1.5 Milligrams |
| Vitamin C | 40 Milligrams |
| Vitamin D | 800 U.S.P. Units |
| Niacinamide | 4 Milligrams |

**Lanteen**



**LANTEEN MEDICAL LABORATORIES, Inc. . . . CHICAGO 10**

# Invitation

**Editor**
Alexander B. Gutman, N.Y.C.

**Advisory Board**
Walter W. Palmer, N.Y.C.
David P. Barr, N.Y.C.
Francis G. Blake,
New Haven, Conn.
Arthur L. Bloomfield,
San Francisco, Calif.
Eugene A. Stead, Atlanta, Ga.
Joseph T. Wearn, Cleveland, O.

**Associate Editors**
Herman Ludwig Blumgart,
Boston. Mass.
A. McGehee Harvey,
Baltimore, Md.
George H. Houck,
San Francisco, Calif.
Chester S. Keefer, Boston, Mass.
T. Grier Miller, Philadelphia, Pa.
Walter L. Palmer, Chicago, Ill.
Oswald H. Robertson, Chicago, Ill.
Ephraim Shorr, N.Y.C.
Russell M. Wilder,
Rochester, Minn.
Maxwell M. Wintrobe,
Salt Lake City, Utah
W. Barry Wood, St. Louis, Mo.
William Smith Tillett, N.Y.C.
George W. Thorn, Boston, Mass.
John B. Youmans, Nashville, Tenn.

THE YORKE PUBLISHING COMPANY, INC.
*also publishers of The American Journal of Surgery*

## SUBSCRIPTION ORDER FORM

THE AMERICAN JOURNAL OF MEDICINE
49 WEST 45TH STREET, NEW YORK 19, N.Y.

Please enter my subscription to the new monthly journal, THE AMERICAN JOURNAL OF MEDICINE. Subscription U.S.A. $10.00 per year. $12.00 Foreign.

NAME_____ ADDRESS_____

CITY_____ STATE_____

*"Infinite riches in a little room"*

8 vitamins in large therapeutic amounts concentrated within a single THERA-VITA* capsule provide the means for highly potent multivitamin therapy in hypovitaminosis — malnutrition — convalescence — old age — anorexia — pregnancy — nutritional anemia.

Each *Thera-Vita* multivitamin capsule furnishes doses adequate for therapeutic requirements of vitamins A, $B_1$, $B_2$, C, D, plus niacinamide, $B_6$ and calcium pantothenate.

*Thera-Vita* capsules are well tolerated and easily swallowed.

One or more *Thera-Vita* multivitamin capsules as prescribed are a convenient and economical means for providing "resultful" vitamin therapy in nutritional disorders.

One *Thera-Vita* capsule contains:

| | |
|---|---|
| Vitamin A (liver oil conc.) | 12,500 U.S.P. Units |
| Thiamine Hydrochloride ($B_1$) | 10 mg. |
| Riboflavin ($B_2$) | 10 mg. |
| Niacinamide | 100 mg. |
| Pyridoxine Hydrochloride ($B_6$) | 1 mg. |
| Calcium Pantothenate | 10 mg. |
| Ascorbic Acid (Vitamin C) | 150 mg. |
| Vitamin D (Activated Ergosterol) | 1,250 U.S.P. Units |

*Bottles of 100's and 250*

Remember, doctor, THERA-VITA capsules are to be prescribed and not simply suggested to your patients. Help us to maintain the professional status of this product and to avoid its indiscriminate use by the laity without medical supervision.

†*Christopher Marlowe (1564-1593)*
**Trademark Reg. U. S. Pat. Off.*

WARNER
ESTABLISHED 1856

WILLIAM R. WARNER & CO., INC. NEW YORK • ST. LOUIS